LUPUS NEPHRITIS

By

Robert C. Muehrcke, M.S., M.D.

Postdoctoral Public Health Fellow in Internal Medicine, Research and Educational Hospitals, University of Illinois College of Medicine; Clinical Assistant, Cook County Hospital; Research Fellow [illegible] Presbyterian Hospital, Chicago

Robert M. Kark, F.R.C.P., F.A.C.P.

Professor of Medicine, University of Illinois College of Medicine; [illegible] Physician, Research and Educational Hospitals and Cook County Hospital; Associate Attending Physician, Presbyterian Hospital, Chicago

Conrad L. Pirani, M.D.

Professor of Pathology, University of Illinois College of Medicine, Chicago

Victor E. Pollack, M.B., M.R.C.P.E.

Research Fellow in Medicine, Presbyterian Hospital; Instructor [illegible] Medicine, University of Illinois College of Medicine, Chicago

BALTIMORE
THE WILLIAMS & WILKINS COMPANY
1957

Reprinted from MEDICINE
Volume 36 Number 1 March 1957

Library of Congress
Catalog Card Number
57-8645

COMPOSED AND PRINTED AT THE
WAVERLY PRESS, INC.
BALTIMORE 2, MD., U.S.A.

LUPUS NEPHRITIS

I INTRODUCTION

Lupus Nephritis describes succinctly and graphically involvement of the kidney in Systemic Lupus Erythematosus (SLE) Etymologically, the term lupus nephritis is far from perfect, since is combines a Latin and a Greek word to describe a clinical and pathologic entity Descriptively it is inaccurate for the face and skin of those who are ill with lupus nephritis have neither the nature nor the qualities of a scarred wolf-bite

Although we have coined ponderous but precise phrases to describe the grave but common renal complications of SLE the words "lupus" and "nephritis" have the virtue of common usage, and this consideration overrides all other aspects of nomenclature "Lupus nephritis," thus named, serves to focus attention on a specific disease of the kidney which is at present the major complication and the most pressing problem in patients ill with SLE The clinical course of the disease was different fifteen years ago when Keith (140) wrote, " renal insufficiency does not play an important role in causing death" At that time patients usually died of a "lupus crisis" or as a result of infection

(92 176) However the introduction and liberal use of antibiotics blood transfusions balanced water and electrolyte therapy and corticotrophin (ACTH) and steroid hormone therapy have apparently prolonged life in those afflicted by SLE With present methods of care many patients with SLE can usually be kept free of symptoms for a considerable length of time only to succumb to a progressive renal failure

Because of the problems raised by the increased incidence of lupus nephritis a study of the renal involvement in SLE was undertaken The use of serial percutaneous renal biopsies (133 199) enabled us to follow the histological evolution of kidney involvement The changing clinical status laboratory data and renal function tests were correlated with the serial pathological changes Thus a continuing study of the pathophysiology and natural history of lupus nephritis was possible Preliminary observations have been reported elsewhere (201 202 226) This communication outlines observations on thirty three patients studied intensively during the past two years and was supplemented by a retrospective study of twenty one cases collected from the post mortem material in the hospitals Departments of Pathology

II REVIEW OF CLINICAL FEATURES

1 INTRODUCTION

Lupus erythematosus was first recognized over 125 years ago In 1827 Rayer (236) described it as a rare form of flux sebace Eleven years later Biett (27) writing in Cazenave and Schedel s textbook called it erytheme centrifuge and described Dartre rongeante qui detruit en surface In 1863 Fuchs (83) called it seborrhagia adultorum There seems little doubt that these diseases are identical with what we know today as lupus erythematosus Isolated observations were reported by other authors It was named hypertrophia folliculorum by Robert Willis (302) inflammatio folliculorum by Erasmus Wilson (303) stearrhoea flavescens by Neligan (205) and acne sebacea by Erichsen (76)

F Hebra (116) and Cazenave (49 50) first outlined the disease clearly and distinctly In 1845 Hebra (115) described it under the name seborrhoea congestive In 1856 in his classic *Atlas der Hautkrankheiten* (116) he depicted two forms of the disease and used the term lupus erythematodes —first coined by Cazenave (48) in his fundamental work of 1851 Neumann (206) in 1863 described the pathology of the skin lesion in this disease

Kaposi (132) in 1872 suggested that there were two forms of the disease and named them lupus erythematosus discoides and lupus erythematosus discretus et aggregatus In the course of his pathologic studies (117 132) he observed specific changes in the connective tissue of the papillary layer of the skin These changes he called hyaloid degeneration Five years later Neumann (207) introduced the term fibrinoid degeneration to describe the change in the collagen fibers which assumed the same staining and structural qualities as fibrin

2 RENAL INVOLVEMENT IN SLE

At the turn of the century renal involvement was recognized in cases reported by Hallopeau (106) Cavafy (47) Galloway and MacLeod (86 175) Little (171) and Short (261) In 1895 Brooke (36) found all the signs of soft white kidneys at the post mortem examination of a woman ill with lupus erythematosus and proteinuria Sequeria and Balean (256) reported ten cases of lupus erythematosus and noted involvement of the kidneys in five Galloway and MacLeod (86) in 1903 and Jadassohn (122) also stressed the frequent affection of the kidneys

Sir William Osler in a number of publications (213 214 215 216 217 218) described the systemic manifestations of a group of diseases which involved the skin and joints His first papers in 1888 (213) and 1895 (214) described cases of Henoch Schonlein purpura By 1904 (216 217) he had described twenty nine patients Only one case a fifteen year old girl fulfilled our criteria for SLE She died in uremia (Case 19) This is the first American description of a case of SLE However Osler did not distinguish this case from others with the Erythema Group of Skin Diseases (214) and it is incorrect to attribute to him recognition of SLE as Tumulty and Harvey have done (291) In his review of Henoch Schonlein purpura Gairdner (84) correctly pointed out that in these papers Osler had delineated the clinical features of Henoch Schonlein purpura[5]

In 1908 Pernet (222) described a case of lupus erythematosus with a rapid and fatal course Protein was found in the patient's urine He collected nine similar cases from the literature and called this group lupus erythemateux aigu d emblee In 1922 Keith and Rowntree (141) reported four patients with lupus erythematosus and nephritis and stressed that nephritis was a common complication of disseminated lupus erythematosus Two years later Libman and Sacks (167) reported the clinical syndrome produced by the atypical verrucous endocarditis of SLE which bears their name They found that there was histologic evidence of renal disease in three of their four patients one of whom died in uremia Baehr (8) in 1931 reported renal complications in seventeen cases of Libman Sacks disease He concluded that the lesions were an expression of

importance of renal involvement in lupus erythematosus and stated that therapeutic measures have had no beneficial effect Daugherty and Baggenstoss (63) reported seven cases of Libman Sacks disease who had nephrotic edema arthritis of varying duration and a rapidly progressive course These patients none of whom had a face rash died in renal failure In 1954 preliminary studies of serial renal biopsies in SLE were reported by Muehrcke Kark and Pirani (201 202 226) and Lister and Baker (170) reported a case of SLE diagnosed by renal biopsy

[5] We wish to thank Dr W W Francis and Dr Lloyd Stevenson of the Osler Library McGill University Montreal for access to Osler's personal papers manuscripts and books

3 URINARY FINDINGS

Protein and formed elements may appear in the urine in patients with SLE when they are acutely ill dehydrated and febrile (110 269) As in other conditions these abnormal urinary findings may be transitory For this reason the exact interpretation of data on urinary findings reported by previous authors is difficult as one is often uncertain as to the permanency and significance of their observations on the urine

On the basis of abnormal urinary findings Montgomery and McCreight (191) reported renal irritation nephrosis or nephritis in 100% of thirty two cases of acute SLE and in 69% of seventy seven cases of subacute SLE Other authors reported that abnormal urinary findings were usually transitory during acute exacerbations The abnormalities disappeared either when spontaneous remission occurred (273) or as a result of therapy (42 110 269) However if urinary abnormalities persisted during the stage of remission then renal damage usually was permanent Ross and Wells (248) who studied thirty four patients with SLE wrote Abnormal urinary findings are so common that in their absence we may justifiably question a diagnosis of lupus erythematosus However Harvey and his colleagues (110) found no evidence of renal disease in 26% of their 138 patients with SLE

Considerable amounts of protein may be found in the urine during acute exacerbations of SLE (140) and Madden (176) felt that persistent proteinuria was of prognostic value as it was found more frequently in the fatal cases Gross hematuria was observed in 6% of 34 cases reported by Shearn and Pirofsky (259) and Soffer (269) reported that microscopic hematuria was often found during acute exacerbations Erythrocytes leucocytes and casts were found in the urine at some stage in the course of SLE in 64% of 44 cases observed by Jessar and his colleagues (127) and in 56% of 279 cases reviewed by them Fishberg (78) observed that clumps of leucocytes were common this finding has led clinicians to make an erroneous diagnosis of pyelonephritis Krupp (158) found a telescoping of the urinary sediment in four patients with lupus erythematosus This telescoped urinary sediment contained elements representing the three stages of glomerulonephritis—the erythrocyte and erythrocyte casts found in the acute stage the oval fat bodies and fatty casts of the subacute stage and the broad casts found in chronic glomerulonephritis

Krupp s observation was confirmed by Miale (185) but Cole (56) reported identical urinary findings in a case of polyarteritis nodosa and Schreiner (255) noted telescoped urinary findings in three proven cases of chronic glomerulonephritis He pointed out that although the finding of telescoped urinary

Vural (102) attempted to correlate urinary findings with renal pathology in a retrospective study of 20 patients who died of SLE They found no correlation of urinary abnormalities with the histologic appearance of the kidneys

4 RENAL FUNCTION

Adequate studies of renal function have been made but rarely (190) Soffer, Ludemann and Brill (269) studied renal function in slightly more than half of their 55 patients with acute SLE and considered that the urine concentration test was the least sensitive of the renal function tests they used They stated that the 15 minute excretion of phenolsulphonphthalein and the urea clearance test yielded the most useful information in assessing the function of the kidney in SLE Azotemia was present in 16% of their patients and was also found in 16% of 216 cases reviewed by Jessar *et al* (127) Soffer and his colleagues (269) observed an elevation of the blood urea nitrogen level in over one third of patients in whom protein or erythrocytes were found in the urine Azotemia was usually progressive and death from renal insufficiency resulted They believed that persistent azotemia was a serious prognostic sign (266)

5 EDEMA AND THE NEPHROTIC SYNDROME

Jessar and his colleagues (127) reviewed the literature on SLE which was published between 1948 and 1952 They found reports of 279 patients and added 44 of their own which had been studied between 1937 and 1952—a total of 323 cases Edema was noted in approximately 16% while Soffer, Ludemann and Brill (269) found edema in 22% of the 55 patients they studied

In 1939 Reifenstein and his colleagues (237) reviewed 17 cases of SLE reported in the literature and added one of their own Retrospectively they diagnosed the nephrotic syndrome in two of these patients We cannot agree that there was sufficient evidence in either case to warrant a diagnosis of nephrotic syndrome The first patient had been reported by Belote and Ratner (21), who found protein and casts in the urine The patient was not edematous and the levels of serum albumin and cholesterol were not recorded Tubular nephrosis was diagnosed at autopsy The second case was reported originally by Tremaine (289) and although the patient had features of the nephrotic syndrome (edema proteinuria hypoalbuminemia) the serum cholesterol level was not elevated Six weeks after the onset of edema the patient died Histologic examination revealed severe glomerular and tubular damage Shearn and Pirofsky (259) noted that four of their patients had a clinical variant of the nephrotic syndrome A post-mortem examination of two disclosed chronic glomerulonephritis Three of the four patients had serum cholesterol levels within the range of normal and in the fourth an initial level of 420 mg/100 ml later decreased to 250 mg This patient was reported in full by Brenner and his colleagues (35) as a case of nephrotic syndrome Daugherty and Baggenstoss (63) observed seven cases with nephrotic edema arthritis of varying duration marked proteinuria and with a rapidly progressive course Subacute glomerulonephritis was found in three and chronic glomerulonephritis in one of the four cases on whom autopsies were done

Bossak and Adlersburg (33) studied the biochemical features of the nephrotic syndrome in a patient ill with SLE They found azotemia low serum proteins normal alpha 2 globulin raised beta globulin and a marked rise in gamma globulin levels The levels of total lipid and neutral fat were greatly increased

the beta lipoprotein was decreased and the cholesterol and phospholipid levels were slightly elevated

6 HYPERTENSION

Hypertension is said to appear late in the course of SLE—usually in the presence of advanced renal disease (102 110) The incidence of hypertension associated with SLE varied from 9% to 214 cases (127) to 12% of 138 cases (110) In more than half of Harvey s patients (110) who had hypertension renal involvement was so severe that nitrogen retention had developed On the other hand blood pressure had always been normal in five patients who died in uremia Soffer and his colleagues (269) reported hypertension in 13% of 55 patients and found that treatment with cortisone and ACTH was not effective in reducing blood pressure levels

III REVIEW OF RENAL PATHOLOGY

1 INTRODUCTION

In the past twenty years Klemperer Baehr and their colleagues have made the most thorough pathologic studies of SLE In 1941 they thought (151) that the changes occurring in collagenous tissues were primarily degenerative in nature They observed differences between SLE and rheumatic fever In rheumatic fever proliferation of fibroblasts was the main feature frequently resulting in Aschoff body formation In SLE on the other hand degeneration of collagen was the predominant histologic finding and the cellular reaction was not a prominent feature (144) In distinguishing between SLE and polyarteritis nodosa they pointed out that in SLE degenerative changes appeared in the small vessels and capillaries while vessels of a larger caliber were usually affected in polyarteritis nodosa The changes in the connective tissues in polyarteritis nodosa were also accompanied by an inflammatory reaction associated with an infiltration of eosinophilic polymorphonuclear cells These changes were not seen in SLE

It is apparent from reading their publications that Klemperer and his colleagues modified their opinions in the course of their studies on the so called systemic 'collagen diseases They came to regard the widespread alterations in the connective tissues as a manifestation of a single process involving not collagen but the ground substance of the heart glomeruli the skin and the blood vessels (148) Histochemical studies by Klemperer s associates Gueft and Laufer (104) indicated that the fibrinoid material seen in the ground substance in SLE includes an unusual protein derived from the degradation of nuclear proteins This protein was later characterized as a paraprotein which appeared as a result of the metabolic defect in SLE (147 148) Klemperer and his coworkers suggested that the paraprotein impregnated the ground substance by translation from the bloodstream into the vessel wall (104 146)

2 GROSS RENAL PATHOLOGY

With regard to the pathologic changes in the kidney, lupus nephritis was found in 28 percent (130) to 100 percent (193 246) of autopsy studies of pa

tients dying of SLE Harvey *and his colleagues (110) found* some degree of renal involvement in 34 of the 38 patients with SLE on whom autopsies were made In most large series of autopsy reports glomerular involvement was *found in over 75 percent (9 246 269 272)* At autopsy the kidneys were usually somewhat larger than normal (12 151) Their surfaces were smooth and in some cases were diffusely mottled with minute petechial hemorrhages (3 151 261) They resembled grossly the appearance of the kidney in acute diffuse glomerulo nephritis or malignant nephrosclerosis (151) Contraction of the kidney is un common in lupus nephritis (193) but was noted in cases of SLE dying with chronic glomerulonephritis (193 272 277)

3 WIRE LOOP LESIONS FIBRINOID AND HYALINE THROMBI

In 23 patients with florid SLE on whom postmortem examinations were done Baehr Klemperer and Schifrin (9) found renal involvement in eighteen They *found glomerulonephritis in two glomerulitis in three and in thirteen they* found that the glomerular loops were stiff and thick These lesions were the most impressive microscopic abnormalities encountered in the kidney Baehr and his colleagues coined the term wire loop to describe the lesions because the rigid walls of the glomerular capillaries resembled rather distinctly loops of bent wire The lesions were characterized by a patchy bright eosinophilic thickening of one or more segments of the glomerular capillaries near the pe riphery of the glomerulus With eosin stains the wire loop material resembled amyloid but did not stain with Congo red or take a metachromatic stain with crystal violet (151 272) The wire loop material was shown to be fibrinoid in Neumann s sense (207) It stained red with Azan deep mahogany brown with Bielschowsky silver stain (151) and red with the periodic acid Schiff reagent (183) When stained with Mallory Heidenhain stain the color varied from red to orange to blue and shades of purple were seen depending on the amount of *fibrinoid swelling of the capillary tuft (3) The wire loop material* did not give the collagen reaction with Von Gieson s or the Masson s trichrome stain (151)

The exact location of the fibrinoid wire loop material in the glomerular *tufts has been a matter of controversy It will probably remain an unsettled* problem as long as the exact histology of the normal glomerular tuft is in doubt Klemperer Pollack and Baehr (151) dissolved wire loop material out of the glomerular tufts with trypsin and found an empty space *between the endothe lium and epithelium* Recently Churg and Grishman (51) have studied the locus of glomerular fibrinoid by phase microscopy and the Mallory Gallego stain Their findings also indicate that wire loop material lies between the epithelial and endothelial basement membranes Thus far electron microscopy (85) has not solved this problem Although it has been emphasized that wire loop lesions were pathognomonic for SLE (9) Klemperer also observed wire loop lesions in five of 43 cases of subacute and chronic glomerulonephritis (151) In addition lesions resembling wire loops have also been observed in eclampsia (3 232) scleroderma (3) dermatomyositis (3), malignant hypertension (3 151) and renal vein thrombosis (231)

Another lesion observed in the kidney in SLE is the "hyaline thrombus." Hyaline "thrombi" were found in a small percentage of those cases in which wire-loop involvement of the kidney was demonstrated. They were seen within the capillary lumen and appeared to blend with the walls. They were refractile, homogeneous, and eosinophilic and had the same appearance and staining qualities as "wire-loop" material. Klemperer and his colleagues (151) originally believed "hyaline thrombi" to be an extreme development of the "fibrinoid" alteration of the capillary wall, but Allen (3) considered them to be verrucal swellings of the glomerular capillary wall.

4. FOCAL NECROTIZING GLOMERULITIS AND ENDOTHELIAL CELL PROLIFERATION

Bizarre and pyknotic glomerular cell nuclei were noted in association with severe "wire-loop" changes. In some areas of gross fibrinoid change, obvious necrotic lesions were seen (151, 264). These changes in the glomerular tufts presented a pathologic picture termed focal necrotizing glomerulitis. These lesions resembled those seen in the focal embolic glomerulonephritis first described by Lohlein (11, 172) in patients who died of subacute bacterial endocarditis. Klemperer (151) believed that focal glomerular necrosis and the "wire-loop" lesions were different grades of the same process. He related the development of the lesions to the intensity of the process and noted that focal necrosis of the capillary tufts might occur in the absence of "wire-loop" change. However, Klemperer pointed out that the development in SLE of focal necrotizing glomerulitis was not related to the presence or absence of verrucous endocarditis of Libman-Sacks.

Stickney (272, 274) studied the kidneys of 15 patients who died of SLE. He observed that the most common pathologic lesion in lupus nephritis was an increase in the number of endothelial cells in the glomerular capillaries. Proliferation of these cells was found in seven of the fifteen cases. He also observed hyaline thickening of the capillary walls in five of the cases, but noted the "wire-loop" lesion in only one.

5. HEMATOXYLIN-STAINED BODIES

Hematoxylin-stained bodies were first observed in the heart valves and valve pockets in patients with atypical verrucous endocarditis (103). These smudgy, diffuse, lavender-staining, amorphous bodies have also been found in the kidneys of patients ill with SLE (149). They were seen lying free in the lumen of the glomerular capillaries (149), in the intertubular capillaries (104), and rarely within the substance of "hyaline thrombi" in the glomerular capillary lumen (51). They were easily distinguishable from pyknotic or lysed nuclei (karyorrhexis). Klemperer found "hematoxylin" bodies in the kidneys from 41 of 45 cases of SLE (145). He and his colleagues did not find "hematoxylin" bodies in acute or chronic diffuse glomerulonephritis, rheumatic or bacterial endocar-
d

them in patients with hyperglobulinemia (66) However most authors believe that hematoxylin bodies constitute a reliable criterion for the diagnosis of SLE in autopsy material (104 150)

The hematoxylin bodies were thought to be derived from the nuclei of fibroblasts macrophages lymphocytes and polymorphonuclear leucocytes (104) They were found to be Feulgen positive methyl green negative and strongly absorbent in the ultraviolet spectrum at 2537 Angstroms When they were treated with trichloracetic acid they were found to lose the ability to absorb ultraviolet rays of the same wave length and to become Feulgen negative (150) The above staining reactions suggested that hematoxylin bodies were composed of depolymerized desoxyribonucleic acid (150 233) Special studies have shown progressive degradation of the desoxyribose nucleic acid of the nucleoprotein and ultimate disappearance of the nucleic acid molecule (104) Morphologically (25) and histochemically (104 150) they were found to be similar to the smudgy purple glomerular hyaline thrombi (34) and to the phagocytized masses seen within the Hargraves s cells (109 149 150)

6 SUBACUTE AND CHRONIC GLOMERULONEPHRITIS

Typical subacute glomerulonephritis with epithelial crescents has been observed in SLE by numerous investigators (63 151 167 272) Daugherty and Baggenstoss (63) associated the histologic evidence of typical glomerulonephritic renal lesions with the clinical development of the nephrotic syndrome in their patients with SLE In this type of glomerulonephritis they found proliferation of the endothelial cells of the capillaries In some instances they also noted fibrinoid necrosis of the basement membrane and wire loop changes

7 INVOLVEMENT OF TUBULES INTERSTITIUM AND VESSELS

Fatty degeneration of the tubular epithelium was seen in the kidneys of patients who had the nephrotic syndrome due to lupus nephritis The fatty vacuolization was associated with changes in the glomeruli (35) In reviewing the literature we noted that interstitial edema was rarely mentioned Focal interstitial infiltration with lymphocytes plasma cells and histiocytes occurred frequently (151) but this finding carried no more significance than in general autopsy material The renal arterioles were not infrequently involved and the lesions of SLE were reported to have been similar to those seen in malignant nephrosclerosis or polyarteritis nodosa (12) Pyelonephritis (180 277) renal abscesses (126 265) renal infarcts (272) and chronic arteriolo nephrosclerosis (245) have been described in association with SLE

IV REVIEW OF THE ETIOLOGY AND PATHOGENESIS OF THE RENAL LESIONS IN SYSTEMIC LUPUS ERYTHEMATOUS

The etiology of systemic lupus erythematous remains unsolved Theories regarding the nature of SLE have followed fashionable trends in medical thought In turn diathesis tuberculosis syphilis and other infectious diseases focal infection auto intoxication from the putrid products of digestion and allergy

have been blamed In recent years it has become popular to incriminate hyper immune reactions to the streptococcus dysfunctions of the pituitary adrenal axis and stressful life situations More recently it was postulated that in patients ill with the collagen diseases the proliferation of plasma cells in the tissues and the elevation of gamma globulin in the serum had pathogenetic significance The effect of the elevated gamma globulin would be to produce systemic injury of the connective tissues For this reason the collagen diseases have been classified as dysgammaglobulinemias (69)

Early observers suggested a variety of local and traumatic causes for the appearance of skin lesions in lupus erythematosus (143) French (53 221) German and Viennese (70 105 157 277) investigators supported the theory that lupus erythematosus was of tuberculous origin Keil (136) in a comprehensive review of this subject showed that this view was untenable He investigated the postmortem reports in the literature and determined that in only 20% was there any possibility of active tuberculosis and in some of these cases the disease was probably inactive prior to the onset of SLE Four years later he was the first to use the term systemic lupus erythematosus (137)

In 1919 Barber suggested that streptococcal infections might be the cause of lupus erythematosus (15 16) Since then many cases have been reported in which streptococci seemed to play a prominent etiological role (173 193 253) Belote considered that the disease was due to an ultramicroscopic agent (20) and Moolton and Clark claimed to have isolated a virus from the blood of patients with SLE (194) This has not been confirmed by other investigators Keith and Rowntree (141) emphasized the danger of removing or disturbing foci of infection if there were signs of activity in the disease Although positive blood cultures have been obtained in the terminal stages of the disease (176)—especially when secondarily invading organisms may be expected to have been present—recent bacteriological studies have not supported the view that organisms cause SLE (101)

Crocker (61) suggested a possible endocrine etiology The preponderance of SLE in women has been attributed to ovarian dysfunction and to pregnancy (157) From a questionnaire submitted to 100 dermatologists it was concluded that pregnancy had no significant effect on the clinical course of lupus erythematosus (73) Rose and Pillsbury (246 247) observed a high incidence of acute disseminated lupus erythematosus in women during active menstrual life and emphasized the occurrence of premenstrual exacerbations of the disease Castration (209) and testosterone therapy (11) have had no beneficial effects on SLE Clinical and laboratory findings consistent with SLE were noted in 15 percent of 128 patients with rheumatoid arthritis and hypercortisonism Half of these patients had evidence of renal involvement as indicated by a blood urea level in excess of 40 mg/100 ml cylindruria persistent microscopic hematuria or albuminuria or some combination of these findings (80)

Klinge (153) was among the first to suggest that allergic or hypersensitivity reactions played an important role in the etiology of a number of diseases characterized by fibrinoid degeneration of connective tissue Fox (79) observed the

onset of SLE following administration of foreign protein Stokes Beerman and Ingraham (276) suggested that infectious allergic agents produced vascular allergic manifestations leading to lupus erythematosus Since then many authors (108 124 239 242 286 298) have stressed that an antigen antibody reaction may cause SLE and other collagen diseases or diseases of reaction A possible relationship to the Shwartzman reaction has been suggested by the recent studies of Brunson and his colleagues (38 39 40) and of Booth Muirhead and Montgomery (32) The widespread use of chemotherapeutic and antibiotic agents has been correlated with an apparent increase in the incidence of SLE and other collagen diseases —in particular, polyarteritis nodosa For example Gold (96) stated that in approximately 87% of his patients sulfonamide or penicillin therapy preceded the onset of SLE However Baehr and Pollack (11) found no valid evidence to support this concept and concluded that the development of SLE was coincidental to chemotherapy or antibiotic therapy Teilum (284) suggested that the features of focal glomerulonephritis in SLE were analogous to other changes which could be interpreted as part of an allergic reaction—similar to the Arthus phenomenon He suggested the possibility that the hypergammaglobulinemia of SLE may be the cause of the renal lesions Teilum also observed certain similarities between SLE and sarcoidosis (285 286) and stressed the relationship between the two

Recently Kurnick (159) has studied the mechanism of the Hargraves's cell phenomenon He concluded that an abnormal factor in the gamma globulin altered the cell membrane This allowed a proteolytic enzyme in Fraction III of serum to enter the cell where it destroyed the protein inhibitor of desoxyribonuclease The uninhibited desoxyribonuclease attacked chromosomal desoxyribonucleic acid which in turn changed into the depolymerized nuclear mass so characteristic of fibrinoid hyaline thrombi and the Hargraves's cell Jadassohn (122 123) Stickney (272 274) Montgomery (190) and others (193) supported the view that some toxic irritating substance produced renal damage (81) No such substance has been isolated Many other etiological factors have been implicated these include nervous fatigue (74) the pleuropneumonia group of organisms (37) hereditary syphilis (221) lead intoxication (174), and a special affinity of the vascular system for the ferments of lymphocytes (87)

The reports (68 119 223 238 257) of a syndrome indistinguishable clinically from SLE occurring during the treatment of hypertensive patients with hydralazine are of some interest to those who believe that SLE is a disease of reaction *involving ground substance and connective tissues* These reports strengthen the hand of those who believe that the upsurge in the diagnosis of SLE is the result of a reaction in certain sensitive individuals to antobiotics and can be related to the widespread use of these agents The fact that the SLE like syndrome subsides completely when hydralazine therapy is stopped indicates that the reaction does not produce the disease SLE *de novo* It may unmask subclinical SLE It may provide a clue to the etiology of SLE but it is quite possible that it is producing a syndrome which we classify as SLE because of our imperfect knowledge of the clinical spectrum of the disease and even more

because of our profound ignorance of its cause Nevertheless, Reinhardt and Waldron (238) found acute collagenous necrosis in the skin biopsy of one of these patients and Dammin *et al* (62) reported a case with LE cells ante mortem and postmortem in whom they found renal splenic and other lesions consistent with SLE

Comens (57) has produced a syndrome resembling SLE by the administration of hydralazine to dogs Hargraves s cells were demonstrated in the peripheral blood of these animals He concluded that pathologic specimens of the kidneys revealed changes consistent with those found in disseminated lupus erythematosus Although fibrinoid degeneration was found in two specimens we cannot agree with this conclusion The wire loop lesion demonstrated does not resemble that seen in biopsy or autopsy specimens from patients with SLE and the lesions more peculiar to lupus nephritis did not occur in the kidneys of these hydralazine treated dogs

In recent years clinicians have become aware of a new organ system in the body—the ground substance (*substance fondamentale* or *grund substanz*) and its associated connective tissues The development of new tests for the study of diseases involving the ground substance does not mean that we have the right to separate etiologically diseases of this organ on the basis of these tests The presence of the Hargraves s cell and its associated phenomena implies to many people a definitive diagnosis of lupus erythematosus but this may not be the case We do not as yet recognize the limitations and usefulness of any single one of the many LE cell tests presently being used and it would be unwise—historically speaking and at the present time—to classify everyone with a positive LE cell test as having systemic lupus erythematosu (129) All of us who are old enough recognize that we treated many patients with positive Wassermann tests for syphilis despite their vehement denials that an opportunity had ever arisen for them to contract this venerable disease We now recognize to our dismay that 30 years after Wassermann described his test we were treating unnecessarily patients who suffered with infectious mononucleosis SLE and other diseases in which the Wassermann reaction was positive Although new instruments and new tests may illuminate a disease process the physician produces iatrogenic diseases when he uses them to make injudicious deductions therefrom—deductions which are invalid because the test is not understood or because its limitations have not been worked out

Unfortunately there is no such thing as a pathognomonic sign or test for any disease There are always exceptions which prove the rule Some now consider that dysgammaglobulinemia is the cause of diseases which affect the ground substance Two hundred years ago it was popular to think of fevers as being the cause of a variety of infectious diseases We now understand that fevers are the result and not the cause of infectious diseases and it may well be that dysgammaglobulinemias are the result and not the cause of diseases of the [illegible]

ogy distinct from that of SLE need be invoked to explain lupus nephritis Serial biopsy studies of the kidney provide a sure and simple method to clarify the histogenesis of the renal lesions It is our hope that in the future the application of physical and chemical methods to renal biopsy specimens may further elucidate the reactions of the ground substance in this disease

V METHODS OF STUDY

1 SELECTION OF PATIENTS

Systemic lupus erythematosus presents itself in many a bizarre guise Its course is variable and is usually characterized by acute or chronic episodic illness followed by partial or complete remissions There are no clinical or laboratory findings peculiar only to this disease In each patient the diagnosis was made on the basis of a broad spectrum of clinical and laboratory findings in which the clinical history was most important Thirteen clinical and nine laboratory criteria were used to validate the selection of patients for this study They are set forth in Tables I to III

Thirty three patients were carefully selected on the medical services of three hospitals (Table I) Fourteen Negroes and nineteen Whites were studied At the time of their entry into the study, the ages of the 28 females varied from 11 to 61 years (average age 28 9 years), and the ages of the five males varied from 15 to 47 years (average age 32 2 years) (Fig 1) Of the thirteen symptoms and signs considered by us to be important clinical characteristics of SLE nine or more were found in 30 patients and in no patient were fewer than seven noted (Table I and Fig 2) At least five of the nine laboratory criteria were observed in 32 of the 33 patients (Tables II and III and Figure 3) Thirty two patients had a face rash and 31 suffered from involvement of their joints Every patient had recurrent bouts of fever and in all the clinical course was characterized by exacerbations and remissions Evidence of involvement of the serous membranes either of effusions into the serous cavities or of recurrent pleuritic and abdominal pains was noted in all patients Enlargement of the liver spleen or lymph nodes was found at some stage of the illness in every patient Characteristically these were associated with exacerbations of the clinical illness and the size of the affected organs returned towards normal as the clinical state of the patient improved

The erythrocyte sedimentation rate (ESR) was invariably elevated Anemia or leucopenia was observed in 28 patients In 31, the serum globulin level was elevated and in every patient the thymol turbidity test was positive Hargraves s cells were found on examination of the bone marrow or peripheral blood in 26 patients

2 THE STUDY OF RENAL FUNCTION

After the diagnosis of SLE had been made the patients were studied in hospital and were followed in a special clinic The function of the kidneys was as

sessed by the following tests

a U nalysis In ery ase ea ly mo n ng spe mens of ur ne were exam ned sl o tly af er col ection by one of us (R C M or V E P) C ean vo ded spec mens from ma e pat ents and cathe er spec mens from female pat ents were exam ned A po t on of eacl spe men s subm tted for ba ter olog c culture Flu ds were re cted fo 1? hou s befo e tle col le t on of the spe men for ur nalys s

The spec fic gra ty of the u ne as te ed at room te nperatu e w th a stan la i z l r non e er Tle p o e n was est mate l sem -q ant at ely u ng tl e u fosal cyl c ac d

per n nute and he on entra ed sed m nt resu ı ended by ag t ng n a fe drops of ur ne It as t en exam ne l m cro op ally w th lo and l gh power m gn fi a on Polar ze l l ght vas u d for he den ficat on of an so rop lipods

b Tes s of Renal Funct on

) *The spec fi g av ty* of t e ne vas measu ed fol ow ng a ı od of 14 hou s of fl d l p at on Fo r spe mens of u ne we e collected and the max mum spec fic g a ty s e o led

U ca cl a a c (188) ve e determ ned for a s ngle two l our pe od An a erage u ne flow of at least 2 ml per m n te as atta ned n most p ents T e esults ve e rej o e l a a pe centage of a e age no mal enal fun t on (5 ml m n 100% wh n tl e ur ne flo v as g e er n 2 n l m n 54 ml m n 100% when the r ne flo s l s than ? ml m n)

) *PSP ex e on* 6 mg of phenolsulfonp tl ale n PSP) was n e ed n ra eno af a wa er lo l h d been g ven 249) The bla l ler was empt ed ompletely 15 m nu es la er and he ex e on of PSP as meası e l on a Coleman Jun o spect opl otomet r

In a fe ns an s meas emen s of effe t e renal pl ma flo (ERPF) glon eru a fil at on (GFR) and t bular ex re o y ma s T n) e e m de bv ng nul n and p-am no h pp a d (PAH) a o d ng to the me hods of Gold ng and Chas (98)

B o l cm al Exam nat ons of tl e Bloo l In all ca es the follow ng b o hem l ex m na t ons of the blood e e done blood c eat n ne b tl e me hod of Pe ers (? 4 b oo l u a n og n b the Con av me hod (58) blood non p ote n n trog n b the me hod descr bed b I o l nd McMeek n 155) se um p ot ns b the Col n me ho l (121 305 T e to l se um hol e o wa de e m ned by a mod fi at on of e B oo netl o l ? 0) tl e th mol t b l t a o d ng to the me hod de r be l by Sl nk and Hoag n l ? 8) Wl en nd d l e serum sod um and po a s um were measu d w l an n ernal s nd d flame pl o ome e o d s we e measu e l b the me ho l of S hales and S l les (254) and tl e CO om b n ng po e t y he me hod o Van S yke and Ne l (?9? The se um ho ne se 186 lete m n l n pa nt neph o c and p e donephrot c sy n l ome

3 I E IATOLOGIC METHOD

A 5 ml s mple of enou b oo l vas ob ne l s ng po a m an l a nmon um oxala e or l e n as an co gul The l em o a est ma ed n and l W n robe he a oc t t e and the ery hro yte sedimenta on rate was meası rd b e n etho l o W n obe 304) I u es we e oun ed n both chambe s of an mp o ed Neuba e l ema tom The oag lat on mes we e measu ed by the mod fied method of Lee an l Wh e 220 an l the l l ed ng t mes by the me od of Duke The p o h omb n t ne n e ed by Q k s one tage method (235) D ect and nd e t Coombs s tes s we e pe fo me l on all pa ents (59)

Exa na on fo Ha g aves Cells Clo ted bloo l or bone marrow was ncubate l fo one half to wo ho The clo was b oken up and the le o ytes were concen a ed and smea ed on les and ta ned w th Wr ght s s a n T e sl d s ve e se h d fo at l ast 5 m nute nder

TABLE I

Clinical data on 33 patients ill with systemic lupus erythematosus on whom renal biopsies were done

Case No	Patient's Initials Sex Age (Yrs)	Duration of Disease: Pre study (yrs)	Duration of Disease: Post study (mos)	Date of Biopsies	Pathologic Diagnosis*	Remittent Clinical Course	Fever	Enlargement of: Lymph nodes	Enlargement of: Liver	Enlargement of: Spleen	Serositis: Pleura	Serositis: Pericardium	Serositis: Peritoneum	Arthritis or Arthralgia	Skin Lesions: Face rash	Skin Lesions: Sensitivity to sunlight	Skin Lesions: Nail and Hair Changes	Myocarditis	Raynaud's Phenomenon	Remarks
	First renal biopsy normal																			
1	N K F 23	2	8	1/[illegible]0/55	N	+	+	+	0	+	0	0	0	+	+	0	0	0	+	Onset Acute hemolytic anemia
2	D McK F 29	15	3	6/18/55	N	+	+	+	+	0	+	0	0	+	+	0	+	0	+	*Myxedema Vague symptoms for 10 years*
3	M Wd F 31	5½	12	9/3/54 1/25/55	N N	+	+	+	+	0	+	0	0	+	+	0	+	0	0	Skin biopsy positive
4	E D F 24	11	18	2/17/54 9/8/54	I N	+	+	+	0	0	+	+	0	+	+	+	+	0	+	Thrombophlebitis Raynaud's phenomenon for 8 years before other symptoms
5	F H F 19	3½	8	1/12/55 5/19/55	N N	+	+	+	+	+	+	+	+	+	+	0	+	+	0	
6	J S F 24	1½	14	7/14/54 11/24/54 5/27/55	N MG N (l f) MG N (l f)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Skin biopsy positive Hyperthyroidism
7	M T F 39	3	23	10/17/53 9/9/54 8/5/55	N N N	+	+	+	+	0	+	+	0	+	+	+	+	0	+	Skin biopsy positive
8	M Wr F 34	3½	11	9/14/54 1/16/55	N N	+	+	+	+	+	+	+	+	+	+	0	+	+	0	Died Acute exacerbation with thrombocytopenia and convulsions
9	J A M 15	9	5	3/[illegible]1/55	N	+	+	0	0	0	+	0	0	+	+	+	+	0	0	Face rash for 9 years before other symptoms Two episodes of hemiplegia Thrombophlebitis

First renal biopsy normal																			
10	M S F 61	2 3/12	13	9 19 54 6 17/55	ne I	+	+	+	+	+	+	0	+	+	+	0	+	+	0	Sjögren s syndrome since 1939 Poly arteritis nodosa on muscle biopsy
11	L D F 13	4/12	14	5 8 54 11 21 54 7/2/55	N N MG N (l g) A	+	+	+	+	0	+	+	+	+	+	0	+	+	0	Died of poliomyelitis
First biopsy proliferative glomerulitis																			
12	H K F 30	5/12	18	2/26/54 9/29/54 5 25/55	I MG (l f) PMG (l f) MPG (l f)	+	+	+	+	0	+	0	+	+	+	+	+	+	0	Skin biopsy positive Rheumatic fever Apical diastolic murmur
13	M W F 21	2 8/12	23	9/29 53 2/1/54 8/10 54 5/26 55	PMG (l g) PMG (l g) PMG N (l g) PMG N (l g)	+	+	+	+	+	+	+	+	+	+	0	+	+	0	
14	M M F 17	1	11	10/15 54 1/31/55	PMG (l g) PMG (l g)	+	+	+	+	0	+	+	+	+	+	0	+	0	+	Tuberculous lung abscess developed while on cortisone
First biopsy membranous glomerulitis																			
15	M M P F 47	11	15	5/17/54 3/19 55	I MG (l g)	+	+	+	+	0	+	+	+	+	+	+	+	+	+	Face rash for 8 years before other symptoms Skin biopsy positive
16	C K M 32	1 1/12	15	6/12 54 6/17/55	MG (l f) MG (l f)	+	+	+	+	+	0	0	0	+	+	+	0	0	0	
17	F W F 48	1 3/12	2	6/20 55	MG (l g)	+	+	+	0	0	+	0	+	0	0	0	+	0	+	
18	M D F 31	1 7/12	8	1/11 55 5/11/55	MG (l g) MG N (l g)	+	+	+	+	+	+	+	+	+	+	0	+	0	0	
19	B J F 11	11/12	14	6/15 54 2/10/55	MPG (l g) MPG N (l g)	+	+	+	+	+	+	+	+	+	+	0	+	0	0	

TABLE I—Continued

Case No	Patient's Initials Sex Age (Yrs)	Duration of Disease: Pre study (yrs)	Duration of Disease: Post study (mos)	Date of Biopsies	Pathologic Diagnosis*	Remittent Clinical Course	Fever	Enlargement of: Lymph nodes	Enlargement of: Liver	Enlargement of: Spleen	Serositis: Pleura	Serositis: Pericardium	Serositis: Peritoneum	Arthritis or Arthralgia	Skin Lesions: Face rash	Skin Lesions: Sensitivity to sunlight	Skin Lesions: Nail and Hair Changes	Myocarditis	Raynaud's Phenomenon	Remarks
First biopsy membranous glomerulitis																				
20	P M F 34	9/12	8	1 3 55	MG (l)	+	+	+	+	+	+	0	+	+	+	0	+	+	0	
21	D B F 44	1 5/12	7	2/26 55 7 1 55	MLG (l g) MGN (l g)	+	+	+	+	+	+	+	0	+	+	+	+	0	0	
First biopsy membranous glomerulonephritis																				
22	J M M 47	11	9	2/28 55 6/16 55 11/14 55	MGN (l g) MGN (l g) MGN (l g)	+	+	+	+	+	+	0	+	+	+	0	+	+	0	Arthritis for 10 years before other manifestations of SLE
23	L S F 33	6	18	7/11/54 10 5 54 2/17/55 9/10/55 1 11/56	MGN (l g) SGN (l g) CGN (l g) CGN (d g) CGN (d g)A	+	+	+	+	+	+	0	+	+	+	0	+	0	+	Nephrotic syndrome Died in renal failure
24	W H M 46	1 1/12	3	6/7 55	MGN (l g)	+	+	+	+	0	+	+	+	+	+	0	0	0	0	Nephrotic syndrome
25	R N F 29	11/12	12	5 26 54 5 9 55	MPGN (l g) MGN (d g)A	+	+	+	+	+	+	+	+	+	+	0	+	+	0	Died with convulsions and coma uremia and electrolyte disturbance
26	J M F 23	2 4/12	2	10 17/53 12/12 53	MPGN (l g) SGN (l g)A	+	+	+	+	0	+	+	+	+	+	0	+	+	0	Died in renal failure
27	M L F 27	3/12	1	4/4 55 5/18 55	MLGN (l g) MLGN (l g)A	+	+	+	+	+	+	+	+	0	+	0	+	0	0	Nephrotic syndrome Died of uremia electrolyte disturbance and hemorrhagic pancreatitis

28	A W F 26	6	0	11 24 54	MPG N (l g)A	+	+	+	+	+	+	+	+	+	+	+	0	+	0	Pseudonephrotic syndrome W R + 3 years earlier Died of myocarditis
First biopsy subacute or chronic glomerulonephritis																				
29	R C F 34	6	15	6 7 54 9/27 54 6 21/55	SG N (l g CG N (l g) CG N (l g)	+	+	+	+	+	+	0	+	+	+	+	+	0	0	Nephrotic syndrome Positive skin biopsy
30	B S F 27	6/12	1	1/18 55 9/10 55	SG N (l g) SG N (d g)A	+	+	+	+	+	+	+	+	+	+	0	+	0	0	Pseudonephrotic syndrome Died in uremia
31	R Z M 21	2 4/12	24	9 18 53 4 23 54 9/17/55	SG N (d g) CG N (d g) CG N (d g)A	+	+	+	+	+	+	+	+	+	+	+	+	0	0	Nephrotic syndrome Died in renal failure
32	B D F 18	3/12	0	11 15 54	SG N (l g)A	+	+	+	+	0	+	+	+	+	+	+	+	+	0	Pseudonephrotic syndrome Died with anuria and uremia
33	D J F 39	15	2	7 18 55	CG N (d f)	+	+	+	+	0	+	+	+	+	+	0	+	0	+	

* N Normal I Inadequate PG—Proliferative glomerulitis MG Membranous glomerulitis PGN—Proliferative glomerulonephritis MGN—Membranous glomerulonephritis SGN—Subacute glomerulonephritis CGN—Chronic glomerulonephritis (f) Focal (l) Local (d)—Diffuse (g)—Generalized ns—Nephrosclerosis A—Autopsy

TABLE II

Urinary findings and tests of renal function in 33 patients with systemic lupus erythematosus

Case No	Patients Initials	Sex and Age (Yrs)	Duration of Disease: Pre study (yrs)	Duration of Disease: Post study (mo)	Date of Biopsy	Pathologic Diagnosis	Proteinuria (Plus Units or gm/24 Hrs)	Microscopic Urinalysis: *RBC*	Microscopic Urinalysis: *WBC*	Microscopic Urinalysis: *Casts*	Non Protein Nitrogen (mg/100 ml)	Urea Nitrogen (mg/100 ml)	Creatinine (mg/100 ml)	Sp Gr ‡ Conc Test Max *Sp Gr*	15 Min Exc PSP (% Total Dose)	Urea Clearance Test (% ANRF)
										First renal biopsy normal						
1	N K	F 23	2	8	1/20/55	N	0	0	0	0	28	9	0.9	1.021*	34	59
2	D McK	F 29	15	3	6/18/55	N	+	6-8	0	Occasional	[illegible]	10	1.0	1.036*	29	56
3	M Wd	F 31	6½	12	9/3 54 1/?5 55	N N	0 0	0 0	3-5 5-8	Occasional WBC (few)	34 27	13 7	1.1 1.0	1.028* 1.026*	33 27	89 103
4	F D	F 24	11	18	2/17 54 9 8 54	I N	0.3 0	0 7	0 7	0 Occasional	26 31	8 11	1.1 0.9	1.028* 1.032*	25 22	100 116
5	F H	F 19	3½	8	1/12/55 5/19 55	N N	0.2 0	0 0	2 4	Occasional Occasional	31 26	9 9	1.1 —	1.026* 1.030*	17 41	53 —
6	I S	F 21	11½	14	7/14 54 11/24/54 5/27/55	N MG N (1 f) MG N (1 f)	0 + 0	0 0 10-12	0 15 5	0 Many granular occasional cellular Occasional	50 36 32	23 17 16	1.0 1.0 1.0	1.032* 1.020* 1.024*	29 21 17	91 62 99
7	M T	F 39	3	23	10 17/53 9 9 54 9/5/55	N N N	0 0 0.4	0 0 5	0 0 3	0 Occasional Occasional	27 29 17	9 13 7	0.8 1.1 0.9	1.034 1.022 1.0?0	50 25 24	72 76 —
8	M Wr	F 34	4½	11	9/14 54 1/18 55 8 23 55	N N D	0 0 +++	0 0 *15-20*	0 3 5 1 2	Occasional Occasional *Granular*	32 24 *31*	12 9 —	1.0 1.2 *1.1*	1.024 1.024* *1.020*	34 31 —	76 112 —
9	I A	M 15	9	5	3/21 55	N	0	0	0	0	27	10	0.8	1.025	32	115
10	M S	F 61	29½	13	8/19 54 6/17 55	ns I	0.6 +	0 0	7 7	Granular Granular oval fat bodies	39 37	19 19	0.9 1.3	1.0?0 1.016*	?7 11	53 38
11	I D	F 13	5½	14	5 8 54 11/24 54 7 2/55	N N MG N (1 g)A	0.4 1.3 +	0 0 0	0 5-8	Occasional 0	27 22 39	8 8 —	0.8 1.0 —	1.020* 1.020* 1.015	48 26 —	?6 150 —

F b y pr at glomer

1	K	F 30		8	54 9 8 5 5 5	PMG PN f) N PC	0 0 0	0 0 6	0 5	0 O C ee d es	3 30 2	3 9 20	2	0 5 0 5 0 5	3 4 2	60 0
3	W	F	29	23	29 5 5 8 5 5 26 55	P G g P G g P C N g P G N g	+ 0	5 2 0 0	5 0 5 0	0 0 0	2 3 3	9 8 5	0 3	030 0 6 0 0	8 0 8 2 6	89 02 8 02
		F			0 5 5	PM g g	2 8	5 0	0 0	I g ee co	6 36		0 9 0 8	02 02	3 2	66 0

Γ b p y mbra mer

5	P	Γ			5 9 55	C g	0 0 8	0 0	0	Occas 0	3 30	5 0	0 0 9	0"0 0"0	25 9	69 9
6	C	2		5	6 5 6		0 0 8	0 0	0 0	0 0	7	2	3 5	030 0 0	29 3	5 5
	C	F 8		2	6 0 55	C g	2 5	2		0	36		3	0	32	
8		Γ		8	5 5 55	G g G N g	9 2 8	0 0	3 0	O ee	35 2	3 6	0 0	0"0 0 8	3	50
9	B	F			6 5 5 0 55	PG g PC N g	0 6	2 0	0 8	0 k	3 3	9	0 9 0 7	0 0	35	
20	P	F 3	9	8		G	0	8	3		3	0	0	0 8	9	—
2	D	F		7	2 26 55 55	PG g G N g	0 +	3-4 0	2 5-	0 G	32 6	2 9	0 8	0 7 0 0	0 0	57 2

Γ b ps m mb g me ph

2	A	4		9	2 8 55 6 6 55 5	G N g A G N g G N g	0 8 0 6 +++	8- 0 0- 5 5- 0	8- 0 0-30 5- 0	y g n la and va g an a y ea d g n	35 3	9 9 2	0 8 3 2	0 8 0 1 0 3	25 26 2	6 52 4

TABLE II—Continued

Case No	Patients Initials	Sex and Age (Yrs)	Duration of Disease: Pre-study (yrs)	Duration of Disease: Post study (mos)	Date of Biopsy	Pathologic Diagnosis†	Proteinuria Plus Units or gm/24 Hrs	Microscopic Urinalysis: RBC	Microscopic Urinalysis: WBC	Microscopic Urinalysis: Casts	Non Protein Nitrogen (mg/100 ml)	Urea Nitrogen (mg/100 ml)	Creatinine (mg/100 ml)	Sp Gr‡ Conc Test Max Sp Gr	15 Min Exc PSP (% Total Dose)	Urea Clearance Test % ANRI
Patients with biopsy—membranous glomerulonephritis																
23	E B	F 33	6	18	7/11 54	MCN (l g)	0	40-50	3-5	Many hyaline granular fatty	35	10	2.6	1.018*	8	11
					10 5 54	SCN (l g)	23	40-50	8-10	Many hyaline fatty cellular	35	17	3.3	1.014*	5.5	13
					2/17/55	CCN (l g)	7.6	25-50	2 5	Many hyaline granular	47	27	4.7	1.012*	4	4
					9 10 55	CGN (d g)	++++	Macroscopic	3 4	Many hyaline granular cellular OFB	61	55	7.9	1.010*	0	0
					1 11/56	CGN (d g A	++++	Many	Many	Many hyaline granular cellular	118	74	13.6	1.010		
24	W H	M 46	1½	3	6 7 55	MCN (l g	0.2	4	3	Hyaline granular cellular	41	18	2.0	1.016*	16	35
25	R N	F 29	½	12	5 26 54	MCN (l g)	1.6	0	8-10	Granular leucocyte	36	15	1.3	1.028	28	55
					5 9 55	MCN (l g)A	3.9	40-50	8-10	Hyaline granular oval fat bodies	150	—	—	1.0 0	25	48
26	S M	F 22	2	2	10 17 53	MCN (l g)	++	5	15	Granular cellular	25	10	0.8	1.020*	28	29
					12 12 53	SCN (l g)A	++++	5	15	Granular hyaline cellular	80	—	—	1.014	—	—
27	M I	F 27	½	1	1/4/55	MCN (l g)	+++	—			—	—	—	—	—	—
					5/19 55	MPCN (l g)A	++++	35	35	Hyaline granular cellular	200	—	—	1.010	—	—
28	A W	F 28	6	0	11 24 54	MCN (l g)A	++++	15-20	5-8	Granular cellular hyaline oval fat bodies	43	24	0.9	1.022	18	40
Patients with biopsy—subacute or chronic glomerulonephritis																
29	R C	F 31	6	15	6 7 54	SCN (l g)	++++	8-10	0	Hyaline granular oval fat bodies	60	37	1.6	1.018*	22	16
					9/27 54	CCN (l g)	+++	2 5	5-8	Hyaline granular oval fat bodies	59	36	1.7	1.015*	17	27
					6 21/55	CCN (l g)	2.3	3 5	0	Hyaline granular fatty	51	31	1.7	1.014*	15	42
30	B F	F 27	9½	1	1/18 55	SCN (l g)	1.2	40-50	40-50	Waxy hyaline granular cellular	47	34	3.1	1.010*	0	—
					2 18 55	SGN (d g)A	+++	Many	Many	Many	81	—	—	1.007	—	—
31	R Z	M 21	2	24	9 18 53	SCN (l g)	2.4	10 20	5-10	Hyaline granular oval fat bodies	66	44	3.2	1.020*	13	57
					4 23 54	CCN (l g)	10	10-15	10-15	Granular cellular RBC oval fat bodies	101	59	8.1	1.015*	7	13
					8 17 55	CGN (d g)A	++++	40-50	6-8	Granular RBC hyaline	216	—	23.5	1.011	—	—

32	B D	F 18	2	0	15 54	SG N (g A	4 2	15–20	8–10	Granular hyaline RBC oval fat bodies	16	5	5 4	1 015	3	14
33	D J	1 39	15	2	18 55	C N (d f	++++	40–50	7 8	Gran ar hyaline cc la broad leucocyte	97	83	3 9	1 012*	4	18

† N No ma I Inade ate PG P ol ferat e gl ner s MG Membra s gl ne ts PG N Pr ferat e g nerulonephr s MG N Membrano s glomeru onephr tis SG N S acute glome l neph t s C G N Chronic glomerulonephritis (f Foc l Lo al (1 I ff se (g Generalized ns Neph osc eros s A Autopsy D Died No autopsy

In t n a n wl ch t e spec fic grav ty once trat n test was done are marked w th an asterisk In other nstances the f gure g en s t e h ghest recorded spec fic grav ty

TABLE III

Other pertinent laboratory data on 33 patients with systemic lupus erythmatosus on whom renal biopsies were done

Case No	Patients Initials	Sex and Age (Yrs)	Duration of Disease: Pre-study (yrs)	Duration of Disease: Post study (mos)	Date of Biopsy	Pathologic Diagnosis*	Serum Cholesterol (mg/100 ml)	Serum Albumin (gm/100 ml)	Serum Globulin (gm/100 ml)	Serum Cholinesterase cΔpH units/hour)	Thymol Turbidity Test	Coombs's Test: Direct	Coombs's Test: Indirect	Wassermann Test	Hargraves's Cells	Hematocrit (%)	WBC (/mm³)	ESR (mm/hour)
First renal biopsy normal																		
1	N K	F 23	2	8	1/20 55	N	2 6	5 3	2 5	—	12 7	+	0	0	+	42	3500	35
2	D McK	F 29	15	3	6/18 55	N	410	4 9	2 0	0 62	5 6	0	0	0	0	34	4400	27
3	M Wd	F 31	6½	12	9 3/54 1/25 55	N N	332 308	5 2 5 1	2 1 3 1	— 0 97	4 7 7 7	0	0	0	0	38 40	4000	25
4	E D	F 24	11	18	2/17 54 9 8 54	I N	179 159	4 6 4 6	2 9 3 2		7 0	+	+	0	 +	41 37	4000	36
5	F H	F 19	3½	8	1/12 55 5 19 55	N N	247 240	3 6 4 3	3 7 3 6	0 54	8 8 4 4	+	0	0	+	40 40	6600 5500	24 34
6	J S	F 24	1½	14	7/14 55 11/24 55 5 27 55	N MG N (1 f) MG N (1 f)	— 3°2 342	3 6 4 1 4 7	3 3 2 6 3 2		3 1 14 5 11 0	+ 0	0 0	0	+	30 42 41	5100 5100 6000	34 34 15
7	M T	F 39	3	23	10 17 53 9/9 54 8 5 55	N N N	240 258 °50	4 4 4 3 3 8	2 9 2 3 3 6		 12 0 13 8	0	0	0	 +	35 41 40	8350 °000 °900	24 31 46
8	M Wr	F 34	4½	11	9/14 54 1/16 55 8/31/55D	N N —	240 390 —	2 9 3 5 4 4	3 4 3 9 4 8	0 60	27 8 3 9	0	0	0	+	32 40 25	12900 14300 20000	43 43 66
9	J A	M 15	9	5	3 21/55	N	240	5 0	3 7		22	0	0	0	0	49	8900	39
10	M S	F 61	2½	13	8/19 54 6 17 55	ns I	290 308	3 2 3 4	3 5 3 4		12 7 9 8	0	0	0	+	39 41	6000 5300	45 43
11	L D	F 18	4½	14	5 18 54 11/24 54 7/12/55A	N N MG N (1 g)	200 150	2 9 3 7	4 0 4 3		13 3 13 ?	+	0	0	+	22 31	3300	34 34

F s b opsy p olifera g meru s																		
2	H K	F 30	3 ₂	18	2 28 54 9 28 54 5 25 55	PMG f PMG f MPC f	2 5 227 21	4 6 4 7 5 1	3 6 3 0 3 2		19 5 10 3 12 7	0	0	0	+	36 42 40	7000 7900 0300	39 38 28
3	M W	F 2	2	23	9 29 53 2 1 54 8 10 54 5 26 55	PMC (I g PMG 1 g) PMG N 1 g PMG N 1 g)	220 3 0 392 3 0	3 8 3 1 3 2 4 1	4 3 2 3 4 3 3 8		22 3 7	+	0	0	+	34 36 32 41	7800	26
14	M M	F 17		11	0 15 54 31 55	P IG g) I M (g	230 3 5	3 5 3 3	4 8 4 0	0 47	22 5	0	0	0	+	3 32	5000	37
F t b psy m mb anous g om u s																		
5	M M P	F 4	1	5	5 7 54 3 9 55	I MG (l g	78 185	6 3 7	3 0 3 0		12 4 13 6	0	0	0	+	3 36	4700 5000	8
6	C K	M 32	1 ₂	5	6 12 54 6 17 55	MC (I f MG (I f	3 0 3 2	5 7 6 1	2 8 3 5		9 7 5 7	0	0	0	+	45 50	0	12 12
17	F W	F 48	1² ₂	2	5 20 55	MG (I g	3 7	3 1	3 7	0 93	4 8	0	0	0	0	39	3900	38
8	M D	F 31	1/₁₂	8	1 11 55 5 11 55	MG I g MG N g	49 346	4 0 3 3	4 3 4 4		6 20 4	0	0	64 Kahn u 32 Kahn	+	35 42	4100 4400	42 43
19	B J	F 11	4/₁₂	14	6 15 54 2 10 55	MPC g MPC N g	246 425	3 8 2 2	4 4 5 7	0 42	16	+	+	0	+	31 30	3 00 6500	42
20	P M	F 34	9/₁₂	8	1 3 55	MG (	184	3 0	4 3		9 4	0	0	0	+	35	5000	36
21	D B	F 44	₂	7	2 20 55 7 1 55	MPG (g MG N g	07 24	3 8 3 9	3 6 5 0		19	0	0	0	+	34 5 38	4000	49
F st b psy m n branous g ome u an ph s																		
22	J M	M 47	11	9	2 28 55 6 6 55 11 4 55	MG N I g MC N I g G N (I g	254 264 210	3 2 2 9 2 6	3 9 3 8 4 6	0 45	0 2 16 4 7 1	0	0	0	+	36 37 34	5400 4400 3700	54 43 30

Case No	Patients Initials	Sex and Age (Yrs)	Duration of Disease: Pre study (yrs)	Duration of Disease: Post study (mos)	Date of Biopsy	Pathologic Diagnosis*	Serum Cholesterol (mg/100 ml)	Serum Albumin (gm/100 ml)	Serum Globulin (gm/100 ml)	Serum Cholinesterase (ΔpH units/hour)	Thymol Turbidity Test	Coombs's Test: Direct	Coombs's Test: Indirect	Wassermann Test	Hargraves's Cells	Hematocrit (%)	WBC (/mm³)	ESR (mm/hour)
First biopsy membranous glomerulonephritis																		
23	F S	F 33	6	18	7/11 54 10 5 54 2/17 55 9/10 55 1/11/56A	MGN (l g) SGN (l g) CGN (l g) CGN (l g) CGN (d g)	425 300 3 6 315 250	2 2 7 3 6 4 2 3 2	2 2 1 7 1 8 2 3 1 4	0 90 0 75 0 83	4 5 3 1 7	+	0	0	0	26 20 25 29 23	4000 7100 600 4100 8000	54 0 29 17 —
24	W H	M 46	1½	3	6 7 55	MGN (l g)	460	2 6	3 6	0 92	4 3	0	0	0	0	30	2800	61
25	R N	F 29	11½	12	5/26 54 5 9 55A	MPGN (l g) MGN (l g)	232 410	3 5 3 4	2 7 3 9		12 3 12 3	0	0	0	+	44 31	10 50 14800	30 3?
26	F M	F 2?	2½	2	10/17 53 12 12 53A	MPGN (l g) SGN (l g)	215	3 0 2 5	4 1 3 9		19 7	0	+	0	+	35	4500	42
27	M Pi	F 27	½	1	4 4 55 5/16 55A	MPGN (l g) MPGN (l g)	— 309	2 0	— 3 7		— 11 2	— 0	— 0	— 0	+	— 27	— 4100	4?
28	A W	F 26	6	0	11/24 54A	MPGN (l g)	165	2 6	3 1		5 0	0	0	+	+	20	4650	54
First biopsy subacute or chronic glomerulonephritis																		
29	R C	F 34	6	15	6/7/54 9 27 54 6 21 55	SGN (l g) CGN (l g) CGN (l g)	420 306 300	2 9 3 1 3 9	1 3 2 9 2 3	1 17	11 2	0	0	0	+	38 34 37	3500 4500 5100	42
30	B S	F 27	5½	1	1 18 55 2/10 55A	SGN (l g) SGN (l g)	136 —	1 7 3 0	3 2 2 1	0 39	9 3	0	0	0	+	41 24	6500 13300	42 26
31	R Z	M 21	2½	24	9 18 53 4 23 54 8 17 55A	SGN (d g) CGN (d g) CGN (d g)	460 344 252	2 4 3 1 4 8	3 0 1 8 1 8		13 1 4 4	0	0	0	+	34 25 19	3900 5000 5000	36 7 7
32	B D	F 18	5	0	11/15/54A	SGN (l g)	132	2 3	3 3		12	0	0	0	+	24	3500	20
33	D J	F 38	15	2	7/18 55	CGN (d f)	123	3 9	3 5		6 6	0	0	0	0	23	000	30

* N Normal I—Inadequate PG—Proliferative glomerulitis MG—Membranous glomerulitis PGN Proliferative glomerulonephritis MGN—Membranous glomerulonephritis SGN—Subacute glomerulonephritis CGN Chronic glomerulonephritis MPGN—Membranous and proliferative glomerulonephritis A—Autopsy D—Died No autopsy (f)—Focal (l)—Local (d) Diffuse (g) Generalized

the low power objective and suspicious cells were examined under the high dry objective A preparation was not called positive if only one or two abnormal cells were found

The Hargraves's cell was defined as a polymorphonuclear neutrophil with one or more large inclusion bodies crowding the lobes to the edge of the cell The typical inclusion body was as large as a normal neutrophil It was homogenous unstructured without a sharply defined border and stained a reddish-violet to purple color with Wright's stain We did not consider related phenomena adequate for diagnosis although they may have been suggestive These phenomena were free bodies of the same type as the inclusion material, some types of bodies surrounded by several neutrophils smaller inclusion bodies in neutrophils, inclusion bodies in leucocytes other than neutrophils inclusion bodies appearing to be within a vacuole or showing lobulation or cleaving

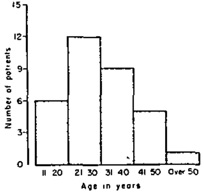


Fig 1 Age distribution of 33 patients ill with SLE studied by renal biopsy

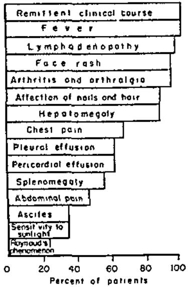


Fig 2 Percent incidence of symptoms and signs in 33 patients ill with SLE and studied by renal biopsy

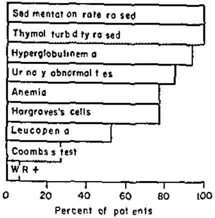


FIG 3 Percent incidence of abnormal laboratory tests in 33 patients ill with SLE who were studied by renal biopsy

4 RENAL BIOPSY AND RENAL PATHOLOGY

After the preliminary studies had been made a renal biopsy was done using the technique previously described The cylinder of renal tissue was fixed immediately in 10% neutral formalin in saline After fixation the specimen was embedded in paraffin and sections were cut at five microns In all cases sections were stained with hematoxylin and eosin (H&E), with Mallory aniline blue (177) and with the periodic acid Schiff reagent (168) A minimum of five H&E sections and one each of Mallory aniline blue and PAS was studied in each case In some cases frozen sections were stained with Oil red O for lipids (168) and in others paraffin sections were stained by the short Foot method for reticulum (168) In a few cases a portion of kidney tissue was fixed by the freezing drying method of Gersh (88) and stained for alkaline phosphatase by the Gomori technique (168)

The criteria commonly in use in pathologic studies were applied to the evaluation of the histologic lesions observed in biopsy and autopsy material The relatively limited amount of material available for study presented new problems which have been discussed in previous papers (133 135 200) Only those biopsies which included adequate amounts of renal tissue were analyzed The tissue was considered to be adequate' when five or more glomeruli and their adjacent tubules were present in the sections in fact most of the biopsies contained ten or more glomeruli

VI RESULTS

1 CLINICAL MATERIAL

Data on 33 selected patients ill with SLE have been summarized in the tables and charts In general the patients have been classified in the tables on the basis of the renal pathology as this provides the most objective basis for study However it has been impossible to divorce entirely the clinical from the patho

logic features, and for this reason the data will be discussed on a clinicopathologic basis

The criteria for selection of patients for study have been outlined in the section on methods The criteria used for selection and an analysis of the signs, symptoms, and laboratory investigations are set forth in Figures 2 and 3 and in *Tables I to IV which also give details of the clinical features, urinary findings* tests of renal function, and laboratory and pathologic data of all patients Definitions of the pathologic terms used are given at the beginning of section VI(2) (page 67)

One-third of the patients were found to have normal kidneys or minimal renal change when first studied, although they had systemic manifestations of the disease This group of 11 patients provides controls in the study, and it is obvious that some time must elapse before we will have an opportunity to report on the development of their disease Already in this group are 2 patients (#6, #11) whose renal disease has progressed—in one case considerably

A Patients with normal renal biopsies

Eleven patients (cases #1–11) have been classified as having normal kidneys—so far as Lupus Nephritis is concerned—at the time of the first biopsy One *of these patients, a 61 year old lady (#10) had benign nephrosclerosis, but* no other lesion in the kidney Another (#3) had had several attacks of acute pyelonephritis Abnormalities were found in the urine of both these patients In three patients the renal biopsies were unquestionably normal, and in five (including #3) minimal changes were detected (See Section VI(2)—Pathology) These were so mild, however that the kidneys have been classified as being normal In three of the patients with essentially normal kidneys slight changes were found in the urinary sediment—usually a few erythrocytes or an excess of leucocytes These findings were usually transient The history of the following case illustrates this point

Case [illegible]

E D (R & L ,05712) an intelligent 26 year old housewife had had multiple joint pains and Raynaud s phenomenon since 1944 In July 1952 she developed severe swelling of the feet following exposure to the sun In August 1953 her joints became swollen She had a fever lost *her appetite and was short of breath The lymph nodes were enlarged* The liver and spleen were not enlarged She had a pericardial effusion The direct and indirect Coomb s tests were positive and the serum globulin was elevated Hargraves s cells were found in the bone marrow After treatment with ACTH was started her clinical condition improved She was discharged from hospital and maintained in health with cortisone Before treatment 3+ protein leucocytes and casts were found in the urine after her temperature was normal and no abnormality was found in the urine

Episodes of arthralgia pleuritic pain and low grade fever occurred In February 1954 the skin of the forearms and fingers was red tense and appeared atrophic There was a diffuse alopecia of the scalp The lymph nodes were again enlarged A renal biopsy was done on February 17 A few leucocytes were found in the urine the GFR (C_{INULIN}) was 114 ml/min and the RPF (C_{PAH}) was 533 ml/min A month later she developed gastroenteritis due to *Salmonella panama* but made an uneventful recovery after treatment with chloramphenicol

TABLE IV

Pathologic analysis of biopsy and autopsy specimens of kidneys from 33 patients all with SLE

Case No	Patients Initials	Pathologic Diagnosis*	Glomeruli: Basement membrane	Glomeruli: Cellularity	Glomeruli: Ischemia	Glomeruli: Hyaline thrombi	Glomeruli: Wire loop lesions	Glomeruli: Karyorrhexis	Glomeruli: Hematoxylin bodies	Glomeruli: Fibrinoid	Glomeruli: Embolic lesions	Glomeruli: Adhesions	Glomeruli: Crescents	Glomeruli: Bowman's space protein	Glomeruli: Glomerular damage	Tubules: Degeneration	Tubules: Atrophy	Tubules: Dilatation	Tubules: Protein	Tubules: Casts	Tubules: Tubular damage	Interstitium: Edema	Interstitium: Fibrosis	Interstitium: Inflammation	Vessels: Sclerosis	Vessels: Fibrinoid
			First renal biopsy normal																							
1	N K	N	±	0	0	0	0	0	0	0	0	0	0	0	0	±	0	0	+	0	0	0	0	0	0	0
2	D McK	N	0	0	++	0	0	0	0	0	0	0	0	+	0	0	0	+	0	0	0	0	0	0	0	0
3	M WJ	N	±	0	+	0	0	0	0	0	0	0	0	0	±	±	0	0	+	0	0	0	0	0	+	0
		N	+	0	+	0	0	0	0	0	0	0	0	0	±	±	0	0	0	0	0	0	0	0	0	0
4	E D	I	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
		N	0	0	0	0	0	0	0	0	0	0	0	+	0	±	0	0	+	0	0	0	0	0	0	0
5	F H	N	±	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0	0	0	0	0	0	0
		N	±	±	+	0	0	0	0	0	0	0	0	0	±	±	0	+	0	0	0	0	0	0	0	0
6	J S	N	±	±	++	0	0	0	0	±	0	0	0	+	±	+	0	0	+	0	+	0	±	0	+	0
		MG N (l f)	+	+	++	0	+	0	0	±	0	0	0	+	+	±	+	0	+	0	+	0	+	+	0	0
		MG N (l f)	+	±	+	0	±	0	0	±	0	0	0	+	+	+	0	0	+	0	+	0	+	0	+	0
7	M T	N	±	0	++	0	0	0	0	0	0	0	0	0	0	±	0	±	+	0	±	0	0	0	0	0
		N	±	0	++	0	0	0	0	0	0	0	0	+	±	±	0	±	+	0	0	0	±	0	0	0
		N	±	0	+	0	0	0	0	0	0	0	0	+	0	±	0	0	+	0	0	0	0	0	0	0
8	M Wr	N	0	±	++	0	0	0	0	0	0	0	0	+	0	±	0	±	+	0	0	0	0	0	0	0
		N	±	±	0	0	0	0	0	±	0	0	0	+	±	±	0	+	+	0	0	0	0	0	0	0
9	J A	N	±	±	+	0	0	0	0	0	0	0	0	0	0	±	0	0	+	0	0	0	0	0	0	0
10	M S	na	+	±	++	0	0	0	0	0	0	0	0	0	++	0	0	0	+	+	+	0	++	0	++	0
		I	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

11	L D	N N MC N (g A	± ± +++	± ± +	0 + +	0 0 0	0 0 +	0 0 +	0 0 0	± 0 +	0 0 0	0 0 0	0 0 0	0 0 +	± ± ++	+ ± +	0 0 0	± ± 0	+ + ++	0 0 0	0 + +	0 0 +	0 + 0	0 0 ++	0 0 0	0 0 +

F s b op y p o f a w g om ul s

2	H I	PMC f I MC f MI ((f	+ + ++	++ ++ +	++ ++ ++	0 0 0	0 0 +	0 0 0	0 0 0	± ± +	0 0 0	0 0 0	0 0 0	+ + +	+ + ++	+ + +	0 0 ±	0 0 0	++ ++ +	+ 0 +	± ± +	0 0 0	± ± +	0 0 0	0 0 +	0 0 ±
1	M W	PMC (g PMG (g I MG N 1 g PMG N g)	+ ++ ++ ++	+ ++ +++ +++	+ + + +	 0 0 0	+ ± ± +	0 + + ±	0 0 0 0	± ++ + +	0 + + 0	0 + + 0	0 0 0 0	+ 0 + +	+ ++ ++ ++	+ + + +	+ + + +	0 0 + +	+ + ++ ++	+ + ++ +	+ + + +	0 0 + 0	± + + +	+ ± + ±	0 + + +	0 ± + ±
4	M V	I MC 1 g PMG (g	+ ++	++ ++	+ +	0 0	0 +	0 0	0 0	+ +	0 +	0 0	0 0	± ++	+ ++	+ ++	0 0	++ +	++ ++	+ 0	+ +	± +	± ±	0 +	0 0	± 0

F b psy membranous g ome u s

5	M M P	I MG (g	++	0	++	0	+	0	0	±	0	0	0	+	++	+	0	±	+	0	+	0	+ ±	0	+ 0	0
16	C K	MC (l f) MC (l f	+ +	± ±	+ 0	0 0	0 ±	0 0	0 0	± ±	0 0	0 0	0 0	0 ++	+ +	± ±	0 0	0 0	0 +	0 0	0 0	0 0	0 0	0 +	0 ±	0 ±
	E W	MC (g	++	0	+++	0	+	0	0	+	0	0	0	+	++	+	0	+	+	0	+	0	±	0	0	±
9	M D	\ G l g MC N (l g	++ +++	± ±	+ +	0 0	+ +	0 0	0 +	+ ++	0 0	0 0	0 0	0 +	++ +++	+ +++	0 +	0 0	++ ++	0 0	+ ++	0 +	+ +	+ +	± +	+ +
19	B I	MI G l g) MPC N (l g	++ +++	+ +	0 +++	0 0	+ +	+ +	0 +	+ +	+ +	+ +	0 0	0 +	+ ++	+ ++	0 0	++ +	+ ++	0 +	+ ++	0 0	0 0	0 0	0 0	± ±
0	P M	MC (	++	0	++	0	±	0	0	±	0	0	0	±	+	++	±	0	+	0	+	0	±	±	0	0
21	D B	MPG (l g) M N (l g)	+ ++	+ ±	+ +	0	0 +	0 0	0 0	0 +	0 0	0 0	0 0	+ 0	+ ++	+ +	0 ++	± 0	+ +	0 0	+ ++	0 +	0 +	0 +	0 +	0 +

I' s b opsy m ml anous glo n u on phri s

22	J M	MC N (l g) MC N (l g MG N 1 g	++ ++ +++	+ + +	+ + +	0 0 0	+ 0 ++	+ 0 ++	0 0 ++	+ + +	++ + ++	± + ++	0 0 0	0 ++ +	++ ++ +++	++ ++ ++	± + ++	+ ++ ++	++ ++ +	+ ++ +++	++ ++ +++	+ ++ +	+ + ++	+ ± ±	0 + +	± ± +

TABLE IV—*Continued*

Case No	Patients Initials	Pathologic Diagnosis*	Glomeruli													Tubules						Interstitium			Vessels	
			Basement membrane	Cellularity	*Ischemia*	Hyaline thrombi	Wire loop lesions	Karyorrhexis	Hematoxylin bodies	Fibrinoid	Embolic lesions	Adhesions	Crescents	Bowman's space protein	Glomerular damage	Degeneration	Atrophy	Dilatation	Protein	Casts	Tubular damage	Edema	*Fibrosis*	Inflammation	Sclerosis	Fibrinoid
First biopsy membranous glomerulonephritis—Continued																										
23	E S	MG N (l g)	++	0	+	0	++	0	0	+	0	0	0	+	++	++	+	++	+	0	++	+	+	0	+	+
		SG N (l g)	+++	++	+++	0	++	±	0	++	0	+	0	+	+++	+++	++	++	++	+	+++	+++	++	++	++	++
		CG N (l g)	+++	+	+++	0	++	0	0	++	0	0	+	+	+++	++	++++	±	+	+++	++++	+++	+++	+++	++	++
		CG N (d g)	+++	++	+++	0	+	±	0	+	0	+	0	0	+++	+++	++	++	+	+	+++	+	+++	++	++	+
		CG N (d g)A	++++	+	+++	0	++	0	0	+	0	++	±	0	++++	+++	+++	++	+++	+++	++++	+	+++	++++	++	0
24	W H	MG N (l g)	+++	+	+++	0	+++	±	0	++	0	0	0	+	+++	++	++	++	+	++	+++	++	++	+	+	+
25	R N	MI G N (l g)	++	++	++	0	+	++	0	+	+++	++	0	+	++	+	0	+	++	0	+	0	+	+	+	±
		MG N (d g)A	+++	+	++	0	++	+	0	++	±	++	0	+	+++	+++	+	0	++	++	++	++	+	±	0	±
26	F M.	MPG N (l g)	+++	++	+	0	++	0	0	+++	0	+	0	+	+++	++	+	++	+	++	++	+	+	+	+	±
		SG N (l g)A	+++	+++	++	±	+++	++	±	+++	+	++	++	++	++++	+++	++	+++	+++	+++	+++	+++	+	+++	0	++
27	M I	MI G N (l g)	+++	+	+++	±	+++	±	++	++	0	0	0	+	+++	+++	+	++	+++	+	+++	++	+	+	+	+
		MPG N (l g)A	+++	+++	+++	+	++	+	±	++	0	++	0	+	++++	+++	++	+++	++	+	+++	+++	+	+	+	+
28	A W	MPG N (l g)A	+++	++	++	+++	+++	+++	++	++	0	0	0	+	+++	++	+	+	+	+	++	+	+	+	+	+
First biopsy subacute or chronic glomerulonephritis																										
29	R C	SG N (l g)	++	+	+	0	++	+	0	+	+	±	0	0	++	++	++	++	++	0	++	++	+	+	+	+
		CG N (l g)	++	+	+++	0	++	0	0	+	0	++	0	+	++	+++	++	++	++	+	+++	+++	++	+++	+	+
		CG N (l g)	+++	±	+++	0	++	0	0	+	0	++	0	0	+++	++	+	++	+	+	++	++	++	+	++	+
30	B S	SG N (l g)	+++	+++	+++	0	+++	++	±	++	+	+++	++	++	+++	++	0	++	+	+++	+++	+++	+	++	+	+
		SG N (d g)A	+++	+++	+++	0	++	++	+++	++++	+	+++	+++	+	++++	+++	++	+++	+	+	++++	+++	++	++	+	+++
31	R Z	SG N (d g)	+++	++++	+++	0	++	++	±	++	+	+++	++	+	+++	++	+++	++	+	++	+++	++	++	+	+	±
		CG N (d g)	+++	+++	+++	0	++	++	±	+	0	++++	++	+	++++	+++	++++	+	+	++	+++	++	+++	++	+	++
		CG N (d g)A	++++	++	++	0	+	±	0	0	0	+++	++	0	++++	+++	++++	++	++	+++	++++	+	+++	++	++	0

32	B D	SG N (l g) A	+++	++	+++	+++	+++	++	+++	+++	+	++	0	+	++++	+++	++	0	+++	++	+++	++	++	+++	++	++
31	D J	CG N (d f)	+++	+	+++	0	+	0	0	+	0	+++	0	+	+++	++	+	++++	+	+	+++	+	+++	++	++	±

*N N r nal I I a le q ate P G I rol fe at e gl n erul t s MG—Men rano s glon ul tis PG N—I ferat e glon e l nep l t s MG N Me l an s g me u p l r t s
SG N Subacute glomerulonephr tis CG N Chron c glomerulonephr tis (f) Focal (l) Local (d) D ffuse (g) General zed ns Nephrosclerosis A—Autopsy

In June 1954 she had a thrombophlebitis of the left leg. Three months later she was readmitted to hospital for study. A butterfly face rash was noted. The lymph nodes were enlarged and there was sclerodactyly. There was *no peripheral edema and the blood* pressure was normal. A renal biopsy was done on September 8. A few erythrocytes, leucocytes and cellular casts were found in the urine. Since that time she has been kept relatively free of symptoms with small doses of cortisone. Examination of the urine has been normal.

First Biopsy. The first biopsy contained normal renal medulla but was inadequate for diagnosis.

Second Biopsy (September 1954). Adequate renal cortex (12 glomeruli) and medulla were included in the sections. The glomeruli were essentially normal. Bowman's spaces contained a moderate amount of proteinaceous material. The convoluted tubules also contained proteinaceous material and were lined by *a slightly swollen and degenerated epithelium.* The interstitial fibrous connective tissue and the small arteries were normal. A very small amount of granular lipid material was seen in the cells of the convoluted tubules in sections stained with Oil Red-O. Gomori preparations for alkaline phosphatase disclosed the presence of abundant enzymatic activity in the cells of the convoluted tubules.

Diagnosis. Essentially normal renal tissue.

The renal histology from two of the patients (#6, 11) was normal at the time of the first biopsy and urinalysis and renal function were not disturbed. Lupus nephritis developed and was found 10 months and 14 months after the first study. One patient died as a result of poliomyelitis, and the other is alive and reasonably well. The histories of these two patients are given below.

Case 6

J.S. (R. & E. 417655), a nervous apprehensive 24 year old housewife had had rheumatic fever in childhood. She enjoyed good health until June 1953 when she developed an erythematous rash involving the face and upper chest following exposure to sunlight. She became acutely ill. A skin biopsy was done. Its histologic appearance was consistent with lupus erythematosus. In May 1954 she was short of breath on exertion and developed Raynaud's phenomenon. One month later she had migratory joint pains and was admitted to hospital. She was febrile, acutely ill, anemic and had a butterfly face rash and alopecia of the scalp. There was tachycardia, electrocardiographic evidence of myocarditis and a pericardial friction rub. The blood pressure was 140/60 mm Hg. There was a pleural effusion and a pleural friction rub was heard. The thyroid gland was diffusely enlarged and a bruit was heard over it. All lymph nodes were enlarged. Urinalysis and tests of renal function were normal. Many Hargraves's cells were found on examination of the bone marrow. SLE and hyperthyroidism were diagnosed. The *BMR* and I^{131} *uptake confirmed the latter* diagnosis. She was treated with ACTH and methimazole and her condition improved dramatically. A renal biopsy was done on July 14. She gained 24 pounds in weight and when discharged from hospital she was free of symptoms and was being treated with small doses of cortisone.

In November 1954 she was readmitted for study. A faint face rash was seen. The skin over the fingers was thickened but the lymph nodes, liver and spleen were not enlarged. There was a trace of protein, many leucocytes and many granular and leucocyte casts in the urine. Renal function was slightly impaired. A second renal biopsy was done.

In January 1955 methimazole *was discontinued but she continued to take cortisone.* Four months later she was again studied in the hospital. There were areas of atrophic skin [illegible]. The skin of the forearm and fingers was tense and atrophic. The blood pressure

glomeruli) were included in the sections. Save for questionable thickening of

membrane the glomeruli appeared essentially normal There was a minimal increase in cellularity of the glomerular tufts and Bowman s spaces contained some proteinaceous material The convoluted tubules were normal in size Their lining epithelium was somewhat swollen and their lumina contained a moderate amount of proteinaceous material The interstitial tissue was not remarkable Minimal thickening was seen in the walls of the small arteries

Diagnosis Essentially normal renal tissue Questionable localized glomerulitis was seen

Second Biopsy (November 1954) Adequate renal cortex (8 glomeruli) but no medulla was included in the sections The glomeruli were slightly ischemic Minimal local hypercellularity was noted and there was moderate local thickening of the basement membrane in several glomeruli Bowman s spaces contained a moderate amount of proteinaceous material The convoluted tubules were normal in size and were lined by a slightly degenerated epithelium In several areas the tubules were atrophic Their lumina contained a moderate amount of proteinaceous material There was a slight increase of interstitial tissue and foci of chronic inflammatory cells were seen Mild thickening and sclerosis was seen in the walls of the small arteries Mallory and PAS preparations confirmed the above findings

Diagnosis Mild local and focal membranous glomerulonephritis

Third Biopsy (May 1955) Small fragments of renal cortex (4 glomeruli) and medulla were included in the sections The glomeruli were slightly ischemic and a slight but distinct local thickening of their basement membrane was noted There was no definite hypercellularity and Bowman s spaces contained no proteinaceous material Minimal degenerative changes were seen in the lining epithelium of the convoluted tubules which contained a small amount of proteinaceous material Mild thickening and fibrosis were seen in the walls of the small arteries

Diagnosis Mild local and focal membranous glomerulonephritis

Case 11

L.D (R & E 4142-44) a 13 year old negro high school student enjoyed good health until January 1954 when she developed migratory arthritis of the ankles and knees One month later she had anorexia was coughing was short of breath and had lost 16 pounds in weight A diagnosis of tuberculosis was made and streptomycin and isoniazid prescribed In March she was feverish and a butterfly rash appeared across the face A diagnosis of erysipelas was made by a physician

On admission to the University of Illinois Hospitals in March 1954 she was anemic febrile lethargic acutely ill and complained of pain in the abdomen The blood pressure was 80/0 There was tachycardia a protodiastolic gallop rhythm and electrocardiographic evidence of myocarditis There was an erythematous rash over the face ears and distal phalanges The conjunctivae were injected and the gums bled easily The cervical lymph nodes and liver were enlarged There were pericardial and pleural effusions There was a trace of protein and several leucocytes erythrocytes and hyaline casts in the urine Many Hargraves s cells were found on examination of the bone marrow She was treated with ACTH and a remarkable clinical improvement took place She became afebrile the pleural and pericardial effusions decreased the gallop rhythm disappeared and the ECG returned to normal Urinalysis and hematocrit became normal A renal biopsy was done on May 8 The GFR (C_{INULIN}) was 117 ml/min the RPF (C_{PAH}) was 668 ml/min and the $T_{M_{PAH}}$ was 76 mg/min She was discharged from hospital on maintenance doses of cortisone

In September she had a cough mild dyspnea pleuritic pain and a sore throat Tender cystic nodules appeared on the dorsal surface of the interphalangeal joints There were pericardial and pleural effusions There was marked improvement of symptoms when the dosage of cortisone was increased Except for mild dyspnea and pericardial pain she was

free of symptoms when admitted for study in October, 1954 Save for a butterfly face rash slight alopecia of the scalp and cervical lymphadenopathy the physical examination was normal The direct Coombs test was positive A second renal biopsy was done when the urinalysis NPN and tests of renal function were normal

In June, 1955 she became lethargic complained of headache and developed fever a stiff neck and a flaccid paralysis of her legs On admission to the hospital her neck was stiff There was weakness of arms and legs and the knee and ankle jerks were absent The CSF pressure was increased the protein was elevated and 225 leucocytes (80% polymorphonuclears) were found in the spinal fluid Poliomyelitis was diagnosed She developed a severe bilateral pneumonia became comatose and died seven days after admission Post mortem examination confirmed the diagnosis of poliomyelitis

First Biopsy (May 1954) Adequate renal cortex (6 glomeruli) but no medulla were included in the sections The glomeruli were essentially normal except for slight ischemia and questionable local thickening of their basement membrane There was slight degeneration of the lining epithelium of the convoluted tubules whose lumina contained proteinaceous material The interstitial tissue and small arteries were normal

Diagnosis Essentially normal renal tissue

Second Biopsy (November 1954) (Fig 4) Adequate renal cortex (8 glomeruli) and medulla were included in the
mal local thickening of the
man s spaces did not contain
dilated They were lined by low cuboidal epithelium in which minimal degenerative changes

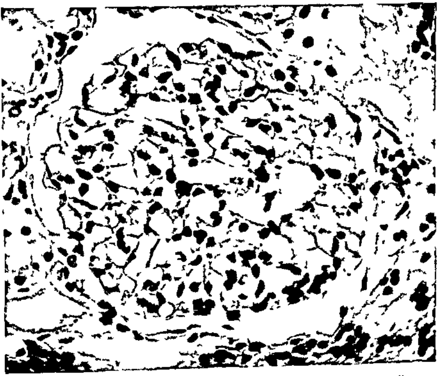


FIG 4 *Patient #11 Second Biopsy October 1954* The glomerulus is essentially normal The patient had been ill with SLE for nine months (H&E × 620)



FIG 5 *Patient #11 Autopsy June 1955* Note the marked and rather diffuse smudgy thickening of the glomerular basement membrane—suggestive of fibrinoid The tubular epithelium is somewhat degenerated (H&E × 400)

were noted The tubular lumina contained a small amount of proteinaceous material The interstitial tissue was normal Comparison with the previous biopsy disclosed no changes of note

Diagnosis Essentially normal renal tissue

Autopsy Specimen (July 1955) (FIG 5) The glomeruli were slightly lobulated and a distinct but mild to moderate local thickening was seen in the basement membrane Minimal local hypercellularity was also noted in the glomerular tufts In places the thickened glomerular basement membrane was smudgy in character suggestive of fibrinoid changes A few wire loop lesions were noted "Hematoxylin bodies were not seen Bowman's spaces contained little or no proteinaceous material Moderate degeneration of the lining epithelium of the convoluted tubules was noted They contained proteinaceous material The capillaries and small veins were congested The interstitial tissue contained foci of chronic inflammatory cells especially numerous around some of the glomeruli and a few small arteries Mallory and PAS preparations confirmed these findings No lipid was seen within the epithelium of the convoluted tubules with Oil Red O preparations of frozen sections Comparison with the previous biopsies indicated a definite increase in the severity of the glomerular changes and in addition the presence of fibrinoid degeneration

Diagnosis Local and generalized membranous glomerulonephritis

B Patients with abnormal renal biopsies

When the first biopsies were made, the histology of the kidneys was abnormal in 22 cases At that time the urine of all but three of these patients (#12 16, 19) was abnormal In general, renal function was not affected until the degree of

kidney damage was severe. In some of these patients the renal lesions and clinical status have changed little during the period of study. In others the renal lesions have progressed and the clinical status has deteriorated. Of the ten patients who died, six died of renal disease (#23, 25, 26, 30, 31, 32), one of renal disease and acute pancreatitis (#27), one during an acute exacerbation of SLE with myocarditis and severe renal damage (#28). One patient died of anterior poliomyelitis (#11). Her kidneys, which had been normal when first studied, were the seat of moderate membranous glomerulonephritis at the time of her death. The tenth (#8) died of an acute exacerbation of SLE; terminally there were abnormalities in the urine, but the last histologic study, made seven months previously, was normal.

The clinicopathologic features of the patients whose kidneys were abnormal will be discussed below under the following headings:

(*1*) Mild Lupus Nephritis (Glomerulitis)
(*2*) Severe Lupus Nephritis (Glomerulonephritis)
(*3*) Nephrotic and Pseudo-nephrotic Syndrome in SLE

(1) Mild lupus nephritis (glomerulitis)—

Ten of the patients had mild involvement of the kidney when first studied. Eight patients were studied on subsequent occasions and a total of 21 studies was made. Initially local membranous glomerulitis was found in the kidneys of *seven patients (#15–21) and proliferative glomerulitis in the kidneys of three* (#12–14). In some of these ten patients mixed membranous and proliferative changes were found, but the cases have been classified according to the predominant pathologic lesion. Clinically none of these patients had severe renal damage when first seen (Tables II and III), and at the time of their last study only one patient (#19) was ill with chronic renal failure. Her renal histology is described below.

The remaining nine patients had relatively good renal function after a period of study varying from 2 to 23 months, but histologically a severe degree of damage was present in at least two (#18, 21). Since they have been under observation all these patients have had symptoms and signs of SLE with a varying clinical course. The disease has been characterized by severe acute exacerbations in three patients (#14, 18, 19) and has been more chronic in character in six (#13, 15, 16, 17, 20, 21). One patient (*#13*) had a number of acute exacerbations when first seen, but the disease has now settled down. To predict renal involvement from the overall clinical course of the patient has proved impossible.

Below are recorded the histories of two of these patients, one (#13) whose renal disease has changed but slowly, the other (#19) whose course has been *more rapidly downhill.*

Case 13

In December 1951, *M. W.* (*R. F. 303519*), a 23 year old negro factory worker, developed an erythematous skin rash on the face, chest and extensor *surface of the forearms.* She had intermittent migratory joint pains. A diagnosis of SLE was made. In August 1952 she developed marked papilledema and diplopia; a cerebral tumor was suspected and a craniot

om) was done No tumor as found It was tho ght that h r symptoms had been due to nvol ement of tl e l a n b SLE Later a pleural effus on vas a) rated She was sl ghtly anem c and had a le ocyto s Ur nal) s s and blood NPN were normal In No ember tl ere was electro a d og aph c e l n e of myocard t s and per card t s The l er and spleen were enla g d Tl ree montl s later sl e de eloped s ell ng of the f ce fe er anorex a st ffness of her finge s and abdon nal pa n She became ery l ort of breatl and was readm tted to l o p tal n February 1953 There were b la ral pleural effus ons and nfiltrat on n the r gl t lo r lobe The e was a m cul r fa e ra h a c tes and enlargement of the l er and lymph node D ffu e alopec a of tl e s alp as noted Prote n leuco yte and cast appear d trans to l) n the ur ne The thymol turb d ty was ele ated and many Harg a es s cells were found on exam nat on of the bone nar ow Tl ere was a pos t e s kle cell phenomenon Treatment w h ACTH re ulted n clin cal mpro ement and she was d scharged from ho p tal on da ly nject ons of ACTH Later sl e as g en co one

In Sep ember sl e was t eated n the ho p tal w l pen c ll n for a pneumococcal pneu mon a A ren l b opsy vas done on September 30 1953 at a t me when r nal) blood NPN and tes s of enal funct on we e normal Four months later she had an exacerbat on of symptoms She was fe e i h had marked dyspnea na sea and vom t ng The pleural cav t es were asp a ed on se eral o cas ons ACTH was g en and her cond on aga n m p oved A se on l renal b opsy was done on F b uary 1 1954 Urnal) s s blood NPN and tests of en l fun t on e normal

Per o l tal e lema was noted n July 1954 Sl e wa adm tted to tl e hosp tal for st d) She l ad a moon fa e and a b te fly face ra h The f nd were normal and the blood p es ure was 128 104 mm Hg The s l en was no enl ged Prote n vas not found n the ur ne but many l u oc te were seen n tl e r nary sed ment The blood NPN and tests of enal fun t on were normal A renal b ops was lone on Augu t 10 1954 Co t sone an l nterm ttent ACTH tl e apy we e g ven wl en she as d scl arged f om l o p tal

In May 1955 the pl ys al examination was normal sa e for a m l l conjun t v t s and the p gmented b tterfl face ra h Ur nal) s blood NPN and tests of renal funct on we e no mal A fou tl renal b op) was done on May 23 1955

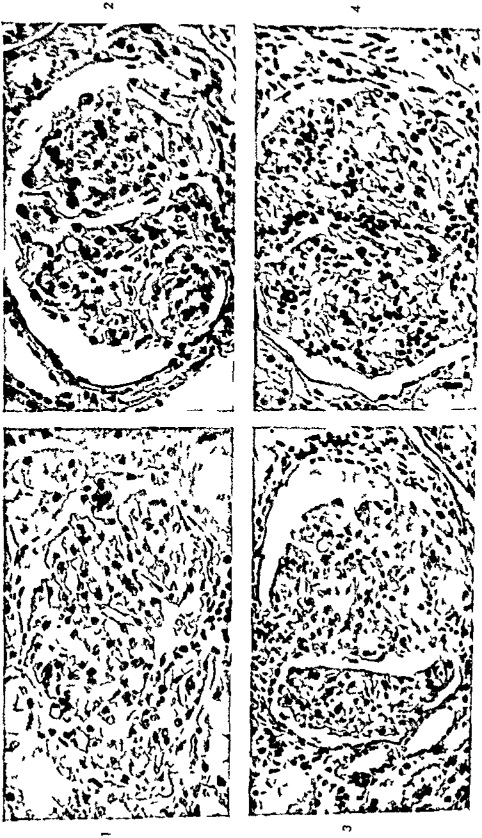
F st B op y (S pten er 1953) A small fragment of r nal cor ex (5 glomeruli) but no medul a was ne ud d n the sect ons The glomerul we e sl ghtly s hem and m n mal to sl gl t rregul r tl kening of the r basement membrane was seen Tl ere was sl gl t local l) per elluli ty b t no a lhes ons we e d tecte l between the glomeru lar t fts and Bowman cap le Bowman s spaces conta ned a small amount of prote n ceous mate al The on olu e l tubules were rregular n s ze they conta ned a mod rate amo nt of p ote na eo mater al and we e l ned by a slightly degenerate l ep hel um Tl ere as a m ld ncrease of nterst t al fibrous connect ve t ssue wh h con a ned a few small foc of cl on nflam matory cells In a few tub les hyal ne casts were present Tl e small arter es vere not rema kable

Diagnosis M ld local and gene al zed p ol fe at e and memb anous glon e ul tis

Se ond B op y (February 1954) (F g 6) Adequate ren l cor ex (18 glome ul) and med l a erc nclud d n tl e sect ons In general th glome ul appeared s l em c an l s gl tl lobula e l an l there was a d st nct local l) percellular y d e to endothel al ell prol ferat on There was m n mal local th k n ng of the b sement memb ane In pl es lhes ons we e no ed between the glomeru ar tufts and Bowman s capsu le b t no ep the al rescents ere p esent Tl e con olute l tubules conta ned a small amount of p ote na eous ma e al and the r l n ng ep theli m was m ldly degenera ed The n erst t al fib o s con nect e t ue as sl ghtly ncreased and onta ned oc as onal l on nfl mmatory ells The sn all bloo l es els were congested and a few red blood cells had a d fin te s kle sl ape No defin e changes were detected n tl e alls of tl e small a ter es

Diagnosis Lo al and gene al z d p ol fe a e and m e b anous glome l tis A l agnos s of s ckle cell tra t was made Tl s confirmed by labo ato y st d es

Th d B opsy (Aug t 19) Adequate renal cortex (16 glomerul) and medulla were n cl ded n the sect ons Tl ere was m n mal scl emia and sl gl t lol ul on of the glomeru l



COLOR PLATE—FIG 1 *Patient #12, First Biopsy, February 1954* Note the small areas of local hypercellularity at the periphery of the glomerular tuft In these areas there is also mild smudgy thickening of the basement membrane (H&E × 400)

COLOR PLATE—FIG 2 *Patient #19, First Biopsy, June 1954* Note there is an irregular rather severe fibrinoid thickening of the glomerular basement membrane This is particularly prominent in the area of local necrosis seen on the right Within this area the capillaries are obliterated, and hypercellularity and karyorrhexis are present (H&E × 430) Compare Color Plate—Fig 3

COLOR PLATE—FIG 3 *Patient #19, Second Biopsy, February 1955* Note the fairly severe irregular smudgy thickening of the basement membrane Above the glomerulus is adherent to Bowman's capsule, near the base of the adhesions poorly defined 'hematoxylin' bodies can be seen (H&E × 430) Compare Color Plate—Fig 2

COLOR PLATE—FIG 4 *Patient #13 Fourth Biopsy, May 1955* Numerous areas of local hypercellularity can be seen throughout the glomerulus There is a slight to moderate irregular thickening of the basement membrane (H&E × 470) See also Fig 6



FIG 6 *Patient #13 Second Biopsy, February 1954* There is slight lobulation of the glomerular tuft Note the smudgy basement membrane thickening and hypercellularity in local areas at the periphery of the glomerulus (H&E × 450) See also Color Plate—Fig 4

Many glomeruli were large and a distinct local hypercellularity was seen Their basement membrane was only slightly thickened in some areas No distinct "wire loop lesions were noted In a few areas within the glomeruli the hypercellularity was very marked and had caused complete obliteration of the capillary lumina Karyorrhexis was noted in these areas No adhesions were seen between the glomerular tufts and Bowman s capsules and no epithelial crescents were noted No 'hematoxylin" bodies were seen The convoluted tubules contained a moderate amount of proteinaceous material Their lining epithelium was mildly degenerated A few hyaline casts were noted within the collecting tubules There was a mild sclerosis of the walls of all the arteries and arterioles When compared with the previous biopsies there was a distinct increase in the severity of the glomerular damage

Diagnosis Local and generalized proliferative and membranous glomerulonephritis

Fourth Biopsy (May 1955) (Color Plate—Fig 4) Adequate renal cortex (13 glomeruli)

in places but only minimal karyorrhexis and no 'hematoxylin' bodies were seen There were no adhesions between the glomerular tufts and Bowman s capsule, nor were epithelial crescents detected There were mild degenerative changes of the epithelium of the convoluted tubules whose lumina contained a moderate amount of proteinaceous material A few hyaline casts were noted within the collecting tubules The interstitial fibrous connective tissue was slightly increased and contained a few scattered inflammatory cells There was a minimal degree of thickening of the wall of the small arteries and mild degenerative changes were seen therein but no fibrinoid was noted Comparison with the previous biopsy showed no differences in the severity of the lesions

Diagnosis *Local and generalized proliferative and membranous glomerulonephritis*

Case 19

In July 1953 *B J (R & E 40o19")* a cheerful 12 year old negro school girl developed pneumonia and a pericardial effusion The pneumonia improved on treatment with penicillin but the pericardial effusion persisted There was a history of intermittent episodes of fever and stiffness of the fingers and toes In August she was referred to the University of Illinois Hospitals She was anemic acutely ill and had a high fever A dark scaly eruption covered the whole thorax The blood pressure was normal The heart rate was rapid and there was electrocardiographic evidence of myocarditis There were effusions into pericardial pleural and peritoneal cavities The liver spleen and lymph nodes were all enlarged Urinalysis was natural The leucocyte count was normal The thymol turbidity was 25 units the cephalin flocculation was 4+ in 48 hours and many Hargraves's cells were found on examination of the bone marrow SLE was diagnosed and treatment with ACTH was started She had a prompt clinical response became afebrile and the pleural and pericardial effusions decreased Cortisone was given after her discharge from hospital

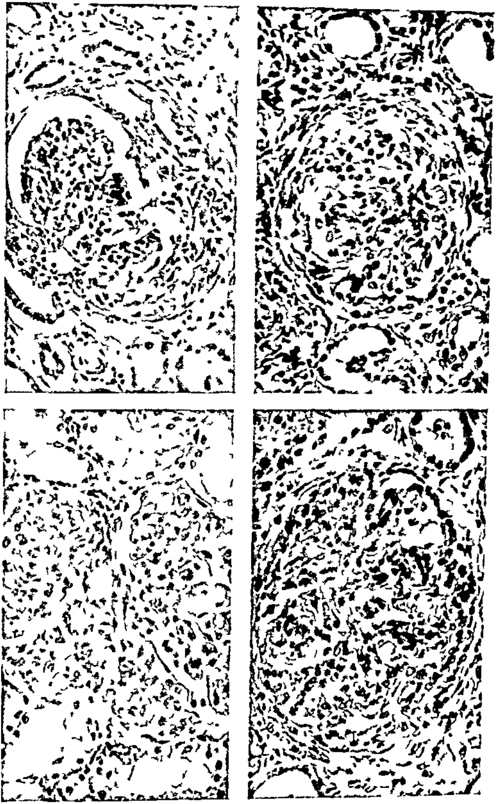
In December 1953 her symptoms returned she was dehydrated had lost weight and

was 33 6 units and the cephalin flocculation was 4+ in 48 hours The blood NPN was normal The GFR (C_{INULIN}) was 98 ml per minute the RPF (C_{PAH}) was 514 ml per minute and the $T_{M_{PAH}}$ was 73 mg per minute A renal biopsy was done on June 14 1954

Over the next seven months increasing amounts of protein were found in the urine In January 1955 she was anorexic and lost 15 pounds in weight The arterioles in the fundi were narrowed The liver was enlarged there was ascites and some peripheral edema Many lymph nodes were enlarged The serum albumin was 2 2 gm and the serum globulin 5 7 gm/100 ml The blood cholesterol was 425 mg/100 ml Gross proteinuria was noted and many leucocytes and granular and hyaline casts were found in the urine Tests of renal function

and medulla were included in the sections Most glomeruli were definitely altered they were somewhat lobulated there was local and smudgy irregular thickening of their basement membrane suggesting fibrinoid changes Wire loop lesions were noted in many

glomerulonephritis of Lohlein In these areas karyorrhexis was noted but no hematoxylin bodies were seen There were a few adhesions between the glomerular tufts and Bowman's capsules but no epithelial crescents were seen The convoluted tubules varied somewhat in size their lining epithelium was slightly degenerated and their lumina contained a small amount of proteinaceous material There was a slight increase in interstitial connective tissue with minimal edema and infiltration of chronic inflammatory cells Mild sclerosis and questionable fibrinoid changes were seen in the small arteries Mallory and PAS preparations confirmed these findings


5 6 7 8

COLOR P E—F G 5 *Pa n #2 B p y O b 1953* F b no d h ken ng of h g om ru b men m n b ne p om n n hro ghout he g om ulus Th e a e no d n t oop H&F × 500) S e al o Co o P e—F g 6

COLOR P E—F G 6 *I a n # A p y D mb 1953* G omerulu f om the au opsy m n of e me a a Co o Pl e—F g 5 No e the l ge f bro p hel al c e nt o up ng m h of Bo m n s s e The g ome ul s omp e ed Hype ellul y and regu h n ng of h g omerula b m n memb ane is p esen No e the b u o o of he edema ous n e al ss e (H&E × 430)

CO OR PLA E—F G 7 *Pa ien #31 F B op y S p mbe 1953* The glome u us s obu ed an l th e a e many a e s of endo h l al ell p o fe at on The b ement membran s ma kedly h k ned and mudgy No the ep h l al cell p ol fe a on at the pe pherv sugg e of ea ly resc nt fo ma on The nte s al t ssue s edema ous H&E × 430 Compa e Co o P e—F g 8 and F g 8 and 9

COLOR PLATE—F G 8 *Pa n #31 S ond B op y Ap l 195* No e he se e e gul th k n ng of h g on eru a b sement memb ane ob a on of p a s nd ea ya n z on F b no d hang w e o s d n o h g om u No the fib o p he n en an l he ed ma and fib osis of he n erst al t ssue (H&E × 430 Compa e Co o P e—F g 7 and F g 8 an l 9

Diagnosis Local and generalized membranous and proliferative glomerulitis

Second Biopsy (February 1955) (Color Plate—Fig 3) Adequate renal cortex (five glomeruli) but no medulla were included in the sections The glomeruli were ischemic and slightly lobulated There were local areas of hypercellularity and of thickening of the basement membrane with the formation of wire loop lesions and in places obliteration of the capillary lumina In some glomeruli the basement membrane was *not only thickened but* appeared smudgy and granular—suggestive of fibrinoid changes In other glomeruli there was karyorrhexis and a few rather poorly defined hematoxylin bodies were seen A few adhesions were noted between the glomerular tufts and Bowman's capsules in which a mild degree of fibroblastic proliferation was seen in places There were moderate degenerative changes in the lining epithelium of the convoluted tubules whose lumina contained some proteinaceous material A few hyaline casts were noted in the somewhat dilated collecting tubules and in the descending portion of Henle's loops The interstitial tissue was normal Minimal sclerosis of the walls of the small arteries was seen These findings were confirmed in Mallory and PAS preparations

Diagnosis Local and generalized membranous and proliferative glomerulonephritis

(2) Severe lupus nephritis (glomerulonephritis)—

Twelve of the patients had severe involvement of the kidney when first studied Eight patients were studied on subsequent occasions and a total of 26 studies was made Initially *local membranous glomerulonephritis was found in* the kidneys of seven patients (#22–28), some of these had proliferative changes in addition Subacute glomerulonephritis was found in the kidneys of four (#29–32) and chronic glomerulonephritis in one (#33) Clinically eight (#23, 24 27, 29, 30 31, 32 33) had evidence of severe renal disease when first seen, and five have died, the other three are ill with chronic renal failure Three of the remaining patients (#22, 25, 26 28) had some evidence of impairment of renal function Two died (#25, 26) of rapidly progressing renal failure two and twelve months after they were first seen A third (#28) died of SLE within ten days The fourth patient (#22) is chronically ill Nine of these patients had generalized edema, and their illnesses are discussed in detail in section (3) Nephrotic and Pseudo nephrotic syndrome in SLE

Below is recorded the history of one patient who died of chronic glomerulonephritis

Case 31

A
tory
wri t
1951
greatly but subsequently he had bouts of fever and arthritis Save for moon face he wa
ell b April Three months later while still taking cortisone he developed chest pain
tal
l a
u
of
ne

was increased

Between September 1951 and his admission to the University of Illinois Hospitals in May 1953 he had received approximately 75 gm cortisone and 25 gm ACTH Large purple

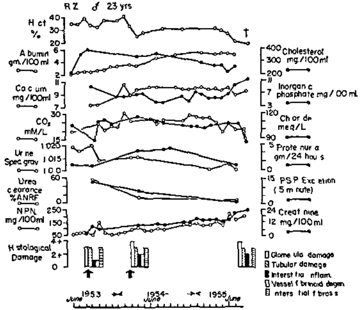


Fig 7 *Patient #31* Chart illustrat ng the histologic changes in two biopsy specimens and one autopsy specimen and the changes in renal function and biochemical findings over a period of 26 months (see text)

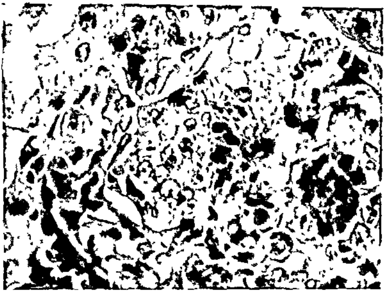
r

r n l on n l m

s a ged from hospital he was chec ... T
sisting of a high protein low salt die
calcium gluconate and sodium bicarb
sea vomiting abdominal pain and d
breathing gran l mal seizures hypertension anasarca and positive Chvostek s sign The liver and lymph nodes were enlarged He was dehydrate l and severely acidotic He was treated with bloo l and intravenous fluids and gra lually improved

In April 1954 he was admitted to hospital for study Neither effusions into the serous cavities nor

His diet was altered to provide 2 000 calories and was low in potassium and protein He was also given sodium bicarbonate aluminum hydroxide gel calcium gluconate oral penicillin and multivitamins He was encouraged to drink large quantities of water especially



9



10

COLOR PLATE—FIG 9 *Patient #3[illegible] Postmortem Biopsy* Photomicrograph of a portion of a glomerulus Note that the glomerular basement membrane is thickened and smudgy The capillary lumina are almost obliterated in the central area Note the hematoxylin bodies and slight karyorrhexis in this area Below and to the right a small hyaline thrombus can be seen (H&E × 1100)

COLOR PLATE—FIG 10 *Patient #26 Autopsy December 1953* This section was stained with Mallory-azan which colors the normal or hyalinized glomerular basement membrane blue In this glomerulus note that the basement membrane is smudgy and stained a reddish color This is typical of fibrinoid In the right lower quadrant small hyaline thrombi are present within the lumina of the capillaries (Mallory azan × 430)

before bed time On this regimen a daily urine output of between 1500 and 2500 ml was maintained

From April 1954 to July 1955, his renal function steadily worsened and severe azotemia developed During this period there were no clinical manifestations of SLE Hargraves's cells were not found in the bone marrow or peripheral blood, the serum globulin and sedimentation rate fell to normal, and the thymol turbidity decreased After sun bathing on July 4 1955, he developed a butterfly face rash fever and swelling of his eyelids, and was admitted to hospital Purpura uremic frost hypertension and enlargement of the spleen were noted He had severe anemia and leucopenia On x ray of the abdomen the kidneys were small and appeared contracted He was again given transfusions of whole blood, and his clinical state improved When readmitted to hospital on August 8 he was short of breath and had been vomiting for three days The blood pressure was 185 115 mm Hg The heart was enlarged and there was a systolic murmur over the precordium The liver was considerably enlarged, the spleen was palpable and there was a generalized lymphadenopathy He was lethargic and restless The hematocrit was 19% There was oliguria and the urinary findings were unchanged He died following two epileptiform convulsions The NPN before death was 212 mg/100 ml

Post-mortem examination revealed the following lesions fibrinous pericarditis and pleuritis perihepatitis and perisplenitis an old mitral valvulitis and fibrinoid degeneration of small arteries in the omentum and wall of the esophagus There was no periarterial fibrosis in the spleen

First Biopsy (September, 1953) (Color Plate—Fig 7) Adequate renal cortex (12 glomeruli) and medulla were included in the sections The glomeruli were ischemic and lobulated Marked diffuse and generalized hypercellularity was seen in the glomerular tufts Their basement membranes were thickened and in some areas were smudgy and granular in appearance and the capillary lumina were obliterated Epithelial crescents were present in many of the glomeruli in others extensive adhesions were seen between the glomerular tuft and Bowman's capsule A few small areas of karyorrhexis were noted but hematoxylin bodies were not found The convoluted tubules were moderately atrophic They contained a small amount of proteinaceous material A few large pale blue-staining hyaline casts were seen in some of the collecting tubules The interstitial tissue was edematous and many chronic inflammatory cells were scattered throughout it There was a marked increase of fibrous connective tissue Fibrinoid material was seen in the small arteries and arterioles whose walls were somewhat thickened These findings were confirmed in Mallory and PAS preparations

Diagnosis Late subacute proliferative and membranous diffuse and generalized glomerulonephritis

Second Biopsy (April 1954) (Fig 8 and Color Plate—Fig 8) Adequate renal cortex (20 glomeruli) and medulla were included in the sections There was profound ischemia and marked lobulation of the glomeruli Most of the glomeruli were either partially or completely fibrosed In some instances this was due to marked thickening of the basement membrane Focal hypercellularity was seen in most of the glomeruli Epithelial crescents were seen in many In places fibrosis of Bowman's capsule was marked The basement membrane was thickened, smudgy and granular, and in places its appearance was suggestive of fibrinoid The convoluted tubules were atrophic They were small, lined by a low cuboidal epithelium, and contained little or no proteinaceous material A few rather large hyaline [illegible]

preparations confirmed these findings

Diagnosis Chronic proliferative and membranous, diffuse and generalized glomerulonephritis

Autopsy (August, 1955) (Fig 9) Many glomeruli were partially or completely hyalinized In others there was marked thickening of the basement membrane which obliterated the capillary lumina in many places 'Wire loop' lesions were seen in a few glomeruli In many there was considerable proliferation of epithelial cells in both visceral and parietal layers of Bowman's capsule A few fibroepithelial crescents were seen and adhesions between Bowman's capsules and glomerular tufts were common The basement membrane in many glomeruli appeared smudgy and granular, but Mallory preparations did not confirm the presence of fibrinoid There was slight karyorrhexis No 'hematoxylin' bodies were seen Most convoluted tubules were markedly atrophic, some were moderately dilated and filled with proteinaceous material or hyaline casts There were advanced degenerative changes in the lining epithelium of these tubules and in Oil-Red O preparations abundant granular lipid was seen in the cells There were similar changes in the loops of Henle and in the collecting tubules There was marked fibrosis of the interstitial tissue which was infiltrated with chronic inflammatory cells The walls of the small arteries and arterioles were severely sclerotic and hyalinized and their lumina were narrowed No definite fibrinoid changes were seen in the vessel walls

Diagnosis Chronic membranous and proliferative, diffuse and generalized glomerulonephritis

(3) Nephrotic and pseudo-nephrotic syndrome in SLE—

The criteria we have used for the diagnosis of the nephrotic syndrome in patients with SLE were the positive criteria of Leiter (166), namely, edema, massive proteinuria, low serum albumin, raised serum cholesterol, and an abnormal urinary sediment By virtue of these criteria and clinical course, seven patients were diagnosed as having the nephrotic syndrome (#19, 23, 24, 25, 27, 29, 31—and Table V) Among the cases from the Pathology files, studied retrospectively, there was one (G B) in whom the clinical data fulfilled all criteria for the diagnosis of the nephrotic syndrome

In contrast to this group of patients there were three edematous patients (#28, 30, 32—and Table VI) whose clinical course progressed rapidly to termination They also fulfilled Leiter's criteria, *save for the fact that their serum cholesterol levels were low* To characterize this group of patients whose illness was so acute and whose prognosis was so grave, we have coined the term "pseudo-nephrotic syndrome" (202) One other case (M O), who died with the pseudo-nephrotic syndrome, was found among the cases studied retrospectively from the Pathology files

A NEPHROTIC SYNDROME Among the patients with the nephrotic syndrome, five were women and three were men Their ages ranged from 13 to 46 years. In two the blood pressure was significantly elevated Three had persistent gross hematuria, and all the others had microscopic hematuria Hyaline and granular casts were found in all, and fatty casts, doubly refractile bodies, or oval fat bodies in five

In general, proteinuria persisted, but the quantity passed varied day by day The nitrogenous constituents of the plasma slowly increased, the concentrating power of the kidney decreased, and there was a parallel deterioration of the urea clearance and PSP excretion The serum cholesterol ranged between 369 and

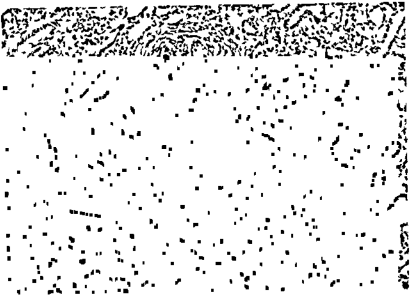


FIG 8 *Patient #31 Second Biopsy April 1955,* Low power view Note edema fibrosis and infiltration of chronic inflammatory cells in the interstitial tissue The tubules are atrophic There is increased cellularity of the glomeruli Epithelial crescents are also seen (H&E × 180) Compare Fig 9 and Color Plate—Fig 7 and 8

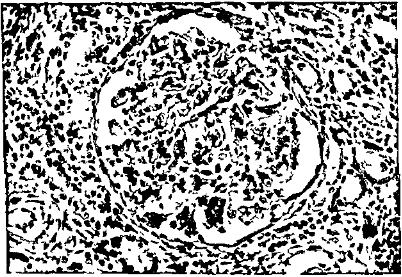


FIG 9 *Patient #31 Autopsy August 1955* Note the severe thickening of the glomerular basement membrane and the irregular distribution of endothelial and epithelial cell proliferation The adjacent convoluted tubules are atrophic and the interstitial tissue is infiltrated by chronic inflammatory cells In other areas fibrosis and hyalinization of the glomeruli were prominent (H&E × 370) Compare Fig 8 and Color Plate—Fig 7 and 8

TABLE V

Clinical and laboratory data from eight patients with SLE and the nephrotic syndrome

Patient	Age Sex	Edema	B P	Urine: Protein*	Urine: Red cells	Urine: Casts	Urine: Fat†	Serum: Albumin	Serum: Cholesterol	Serum: Cholinesterase	Onset of Edema	Present Status
								gm/100 ml	mg/100 ml	Δ pH units/hr		
#19 B I	13 F	+++	110/80	++++	Micro	Hyaline Granular	Nil	2.2	425	—	January 1955	Alive Azotemia and hypertension
#23 I S	33, F	++++	160/90	7.6–23.0	*Gross*	*Hyaline* Granular RBC	*Casts* DRB	*2.7*	*425*	*0.90*	March 1954	Died January 1956 Renal *failure*
#24 W H	46 M	+++	150/90	9.2	Micro	Hyaline Granular Cellular	Nil	2.6	460	0.92	June 1955	Alive Chronic renal failure
#25 R N	[illegible]9 F	+++	180/120	3.9	Gross	Hyaline Granular	Casts DRB	3.4	440	—	April 1955	Died May 1955 Renal failure
#27 M P	27 F	++++	132/ 8	++++	Gross	Hyaline Granular Cellular	Nil	2.0	369	—	January 1955 During pregnancy	Died May 1955 Renal failure and acute pancreatitis
#29 R C	31 F	++++	144/9?	++++	Micro	Hyaline *Granular*	Casts *DRB*	2.9	420	1.17	September 195	Alive Chronic renal failure
#31 R Z	[illegible]1 M	++++	140/108	2.4–10.7	Micro	*Hyaline* Granular RBC	*Casts* DRB	*2.4*	*480*	—	May 1952	*Died August,* 1955 Renal failure
G B ‡	22 M	++++	110/5	++++	Micro	Hyaline Granular RBC WBC	Casts DRB	2.1	471	—	April 1954	Died June 1954 Renal failure

* Grams per 24 hours or plus units
† *DRB = doubly refractile bodies*
‡ Case studied postmortem only

471 mg/100 ml and in none did it exceed 500 mg/100 ml. As we shall show below, the development of the renal lesions in this group of patients—as in other *patients with lupus nephritis—was associated with a suppression* of many of the manifestations of SLE. In particular we have confirmed Brenner's observation (35) that skin lesions may be absent in the presence of the nephrotic syndrome. *Three of these patients are alive (three months to three years after the onset)* and two are slowly becoming increasingly azotemic. The other four died from two months to three years after the onset of edema. All died as a result of their kidney disease, *except patient #27 who suddenly developed acute pancreatitis* when she was already severely ill from renal failure.

At the time of the initial histologic study, membranous glomerulonephritis was seen in four, subacute *glomerulonephritis in three. Case #19 developed* the nephrotic syndrome at the time of her *second* biopsy which showed membranous and proliferative glomerulonephritis. When serial histologic studies were done (*#23, 25, 27, 29, 31*) the lesions were *found to have progressed in all*

TABLF VI

Cl n al and labo ato y data fro fo r pat ents with SI E and the pse lo nephrot s jnd o e

Pa n	Age Se	Edema	B P	Urine: Pro t n	Red Ce s	Ca s	Fa	Serum: A bum n gm 00 m	Cho es ol mg 00 m	Ch nes rase ΔH un s h	Onse of Ed ma	Da e and Cause of Dea h
#28 A W	26 F	+++	2 80	++++	3 o	Ce u a Hya ne Gran la	DRB OFI	2 6	65		No em be 954	Novem be 954 Lu us s
#30 B S	2 F	+++	1"0 0	+++	Gross	Hya ne C anu a Ce n	Waxy Cas s DRB	1 7	6	0 38	Octobe 1954	Fe ruary 955 Rena fa l re
#32 B D	18 F	+++	40 80	4 2	Cross	Hya ne G anula RBC	DRB OFB	2 3	132		J y 1954	No em e 1954 Rena fa ure
I O t	I	++++	0 5	+++	M c o	Granu ar Hya ne	N	2 4	08		lay 19 0	June 940 Rena fa re

C ams pe 24 h s or p s un a
DRB = doub y ref ac e bod es OFB = o a fa bod es
Case stud ed pos m en on y

cases In cases #23 an l 27 membranous glomerulonepl ritis progressed to sub acute glo r erulonepl ritis

The points lescril e l above are illu trated in tl e following cases

Ca e 3

S n e 1949 *F S I (E I 95 I)* (F g 10) a ple nt n l cooper e 33 year ol l house w fe had ha l Rayn d s pl enon enon In m l De e nber 1953 sl e leveloped an eryt ema to s ra h of tl e f e e k and ex ensor surfa e of the forearms Tl s d sappeared w th n two weeks Later tl at n ontl e lo elop l a se ere sore throat an l fe er and generalized lymj l ad nopatl was note l These s gns an l sympto ns sub led spontaneou l w tl n two weeks In F bruary 1954 sv ell ng of the left ankle occ rre l and tl ere we e pa ns n tl e sho l l rs elbo s and knees Edema appeared and progressed to nvol e feet f e an l l nd

On M r l 23 sl e l ec me u ely ll and was adn tted to ano l er ho t tal Sl e l a l fe er generalized e l m an l an enl rge l spl en Tl e blood pres ure was 120 0 mm Hg The l en a ocr t wa 3 ~ and tl e le cocyte count 4 000 mn ³ Tl ere was g oss p o nur an l m roscoj l n a rn Tl e ne spe fic gra t was 1 02 Tl e total serum prote n was 4 0 gm 100 n l Tl e Wa e n ann test was negat e No Targra ess ells ere found on ex an na on of tl e bone n a ro Sl e l ad p so l s of pleurit c pa n The fe er ed a an l sj l no galy s l le l spontaneousl She was sent l ome to re t in bed G oss hematur a l lope l an l n June sl e not l tl at l er l a r was fall ng o t

One n o th later sl e was a ln tte l to the U n vers t of Ill no s Hosj tals Sl e was a e m e tl ere was l ffness n ler the eyes the lympl no les were sl ght l enlarged but the l ver an l spleen were not palj ble Tl e blood pres ure and opt c fund were normal A s sto e m r n r was l ear l at tl e apex Gross l em turia w s note l and 7 gm prote n was

TABLE V

Clinical and laboratory data from eight patients with SLE and the nephrotic syndrome

Patient	Age Sex	Edema	B P	Urine: Protein*	Urine: Red cells	Urine: Casts	Urine: Fat†	Serum: Albumin	Serum: Cholesterol	Serum: Cholinesterase	Onset of Edema	Present Status
								gm/100 ml	*mg/100 ml*	*Δ pH units/hr*		
#19 B J	13 F	+++	110/80	++++	Micro	Hyaline Granular	Nil	2 2	425	—	January 1955	Alive Azotemia and hypertension
#23 I S	31 F	++++	160 90	7 6-23 0	Gross	Hyaline Granular RBC	Casts DRB	2 7	425	0 90	March 1954	Died January 1956 Renal failure
#24 W H	46 M	+++	150/90	9 2	Micro	Hyaline Granular Cellular	Nil	2 6	460	0 02	June 1955	Alive Chronic renal *failure*
#25 R N	29 F	+++	180/120	3 9	Gross	Hyaline Granular	Casts DRB	3 4	440	—	April 1955	Died May 1955 Renal failure
#27 M P	27 F	++++	132/78	++++	Gross	Hyaline Granular Cellular	Nil	2 0	369	—	January 1955 During pregnancy	Died May 1955 Renal failure and acute pancreatitis
#29 R C	34 F	++++	144/92	++++	Micro	Hyaline Granular	Casts DRB	2 9	470	1 17	September 1952	Alive Chronic renal failure
#31 R Z	21 M	++++	140/108	2 4 10 7	Micro	Hyaline Granular RBC	Casts DRB	2 4	460	—	May 1952	Died August 1955 Renal failure
G B ‡	22 M	++++	110/75	++++	Micro	Hyaline Granular RBC WBC	Casts DRB	2 1	471	—	April 1954	Died June 1954 Renal failure

* Grams per 24 hours or plus units
† DRB = doubly refractile bodies
‡ Case studied postmortem only

manifestations of SLE In particular we have confirmed Brenner's observation (35) that skin lesions may be absent in the presence of the nephrotic syndrome Three of these patients are alive (three months to three years after the onset) and two are slowly becoming increasingly azotemic The other four died from two months to three years after the onset of edema All died as a result of their kidney disease, except patient #27 who suddenly developed acute pancreatitis when she was already severely ill from renal failure

At the time of the initial histologic study, membranous glomerulonephritis was seen in four, subacute glomerulonephritis in three Case #19 developed the nephrotic syndrome at the time of her *second* biopsy which showed membranous and proliferative glomerulonephritis When serial histologic studies were done (#23, 25, 27, 29, 31), the lesions were found to have progressed in all

systol c murm r o er tl e precord m The l er spleen and lymph nodes were not enlarged Ur naly s was unchange l The ur ne spec fic grav ty was fixed at 1 010 The blood NPN an l blood creat n ne had increased to 41 and 4 7 mg/100 ml respect ely Sl e had hyper cl lorem c ac do s (CO 16 mM/L cl lor de 12? meq/L) Tl e serum alb m n was 3 6 and tl e glol ul n 1.8 gm/100 ml The ser m cl oles erol was 3?6 mg 100 ml Many *E col* an l *h olyt c e tc o o c* w e cultured f om tl e ur ne A renal b opsy was done on February 7 1955

Fo th a l ss on to the hosp tal In July 1955 l er cl n cal cond t on vas unchanged She l ad azotem a and hyperel lo em c ac do s The l ver and spleen were aga n enlarged Cross hematuria pers sted Sl e became short of breath and compl ned of t redness and was ad m tted to hosp tal v th a l ematocr t of 19% These symptoms mp o ed after tran fus on of one l ter of l lood Tl e ur nary find ngs ere unel anged but tl e blood creat n ne l a l r sen to ?9 mg/100 ml an l tl e non prote n n t ogen to 61 mg/100 ml A fourth renal b opsy was made on September 10

F fth a l s on to the l osp tal From September to No ember 1955 she had se ere menor rl ag a and as se r ly anem c She ha l dyspnea on exert on paroxysmal nocturnal dyspnea an l compla ne l of se ere l ead ches On exam nat on the blood pressu e was 210/110 mm Hg the l e rt wa enlarged Exudates and l emorrhages and sl gl t pap lledema were noted n tl e opt c fun l Tl e hematocr t was 20% the bleed ng t me was prolonge l to 10½ m n tes an l tl e protam ne t rat on was in rea ed nd cat ng the pre ence of a poss ble l epar n l ke r ulat ng ant oagul nt Tl e bloo l creat n ne w s 9 7 mg 100 ml and the CO omb n ng power was 17 mM l er Sl e was treated w th a low so l um low prote n d et pentol n um reserpine an l cl lorpromaz ne

Final a l n on to the hosp tal was n December 1955 Sl e ha l been om t ng for one week Tl e l er and spl en were no longer palpable The ur ne conta ned prote n 4+ many ery h ocytes 5 8 le o es and many granular and cellular ca ts *P ote s r ab l* an l *en e ococ* were ul u l f om it The blood creat n ne was 11.8 mg 100 ml and the blood NPN was 105 mg 100 ml Sl e had an ep sode of acute lup s per ton t s with adynam c leus (2?9) Tl s re ponded ell to treatment w l intra enous l y lrocort sone 600 mg da ly Tl ereafter l er cond t on g a lually deter orated and she d ed on January 11th 1956

At the po t mo tem exam nat on tl ere was serofib nous per card t s an l pleur s gen eral zed e lem a and anasarca The left entr cle vas enlarged an l l er an l spleen were both enl rged Tl e k lne s were moderately contracte l and there was a b lateral p elonephr t s and cyst t s

F st B op y (July 1 5 Ade uate renal co tex (5 glomerul) and medulla were ncl led n the sect ons A lo l mo lerate th cken ng of tl e ba ement membrane of tl e glomerul was seen Tl s appear d some hat smudgy in pl ces W re loop les ons were noted but tl ere was no lear t e dence of fibrino d cl ange in the basement membrane Ne ther l ypercell lar ty of tl e glomerul nor adl es ons were noted A small amount of prote naceo s mater al w s p sent tl n Bowman s spaces The l n ng ep thel um of tl e convol te l t b les as mo l rately leg nerate l and a small amount of pro e naceous material vas seen n tl e r l n n In er t al fibro s and edema were sl gl t M n mal h al ne cl anges were seen n tl e walls of tl e small blood vessels

Da gno I ocal and gen al zed m mb a o s glon r lonephrit s

S cond B op y (October 19?) (F g 11) Adequate renal cortex (glomerul) an l medulla were l ded in tl e sect ons Tl e glon eru l were profoundl altere l w th rather se ere isel em a lob lat on and hypercellular ty Tl e basement membrane was moderately th kene l an l sm lgy s ggest ng w e loop les ons There were a few adl e ons between tl e glon eru l r t f s an l Bowman s caps les but no ep tl el al cres ents were noted In an o ca onal glo erulu karyorrl ex s was seen but no hematoxyl n bod es were present A very small amount of prote naceous material was present n some of Bowman s spaces. Tl re was a rather marke l atropl y of the con oluted tubules whose lin ng ep thel m wa n od r l to se erel leg ne e l The t l lar l m na on a ned a moderate amo nt

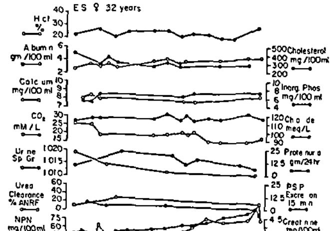


FIG 10 *Patient #23* Chart illustrating the histologic changes in four biopsy specimens and the changes in renal function and biochemical findings over a period of 15 months The patient died in January 1956 (see text)

found in a 24 hour urine specimen Many leucocytes and numerous hyaline granular and fatty casts were seen in the sediment The hematocrit was 21%, the leucocyte count was normal and the ESR was raised The blood NPN and BUN were 41 and 21 mg/100 ml [illegible]

157 ml/min, and the $T_{M_{PAH}}$ was 7 mg/min She was kept in bed the sodium in her diet was restricted but she received no steroids A renal biopsy was made on July 11 Gross hematuria persisted

Second admission to the hospital In September she became feverish had abdominal pain and a recurrence of ankle edema On readmission to the hospital anasarca and pallor were noted The blood pressure was 160/90 mm Hg There was a right pleural effusion and ascites The liver was tender and both liver and spleen were enlarged The left ankle was painful red and swollen The hematocrit was 20% There was gross hematuria and proteinuria Many leucocytes doubly refractile bodies hyaline granular fatty and erythrocyte casts were found in the urine Renal function was severely impaired The NPN and BUN were slightly raised The total serum protein was 5 4 gm/100 ml (albumin 3.5 globulin 1 9 gm/100 ml) The serum cholesterol was 375 mg/100 ml The Coombs and Wassermann tests were negative The thymol turbidity was 4 7 units *F coli* and an *hemolytic enterococcus* were grown from the urine She was kept in bed, the sodium in her diet was restricted and tetracycline was given Marked improvement followed Her temperature became normal The spleen and liver were not palpable The edema subsided and the urine became sterile A renal biopsy was done on October 5

Third admission to the hospital At the time of the third admission to hospital in February 1955 she had malaise and persistent gross hematuria There was periorbital edema but no ankle edema She was pale The blood pressure and optic fundi were normal There was a



FIG 12 *Patient #3 Third Biopsy February 1955* The glomerular basement membrane is diffusely thickened and "wire loops" are seen in places There is no glomerular hypercellularity Note the fibroepithelial crescent in the glomerulus on the right The interstitial connective tissue is edematous fibrosed and infiltrated by numerous chronic inflammatory cells The tubules are atrophic (H&E × 225)

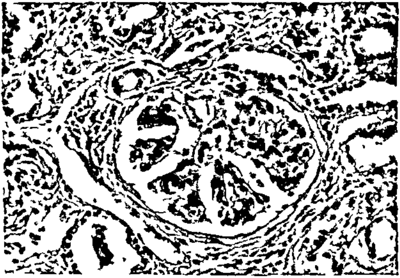


FIG 13 *Patient #3 Fourth Biopsy September 1955* The glomerulus is lobulated Note the smudgy thickening of the glomerular basement membrane and the clumping of endothelial cells The interstitial tissue is fibrotic and edematous The tubules are atrophic (H&E × 430)

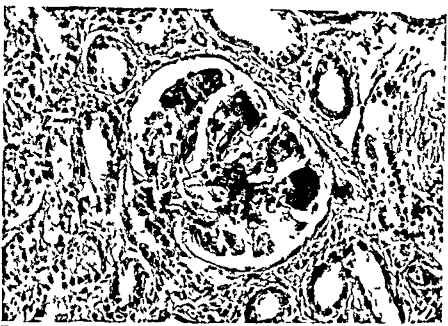


FIG 11 *Patient #23 Second Biopsy, October 1954* The glomerulus is lobulated Note the endothelial cell proliferation and smudgy basement membrane thickening in areas throughout the glomerulus The interstitial tissue is edematous and the tubules are somewhat atrophic (H&E × 430)

of proteinaceous material Hyaline casts were noted within some of the collecting tubules The *interstitial fibrous connective tissue was rather markedly increased and edematous* and was infiltrated by a considerable number of chronic inflammatory cells In places changes suggestive of fibrinoid were seen in the small arteries

Diagnosis Subacute local and generalized, membranous and proliferative glomerulonephritis and superimposed interstitial nephritis

Third Biopsy (February 1955) (Fig 12) A small fragment of renal cortex (3 glomeruli) but no medulla was included in the sections The glomeruli were somewhat lobulated and markedly ischemic A diffuse somewhat smudgy thickening of the basement membrane

degenerative changes of the lining epithelium were seen They contained a relatively small amount of proteinaceous material and in places a few hyaline casts The interstitial fibrous connective tissue was markedly increased and edematous It was infiltrated by a large number of chronic inflammatory cells There was moderate thickening and sclerosis of the walls of the small blood vessels

Diagnosis Early chronic diffuse and generalized membranous glomerulonephritis with superimposed interstitial nephritis

Fourth Biopsy (September, 1955) (Fig 13) Adequate renal cortex (7 glomeruli) and medulla were included in the sections The glomeruli were ischemic and lobulated and a rather severe and diffuse thickening of their basement membrane was seen There was local hypercellularity 'Wire loop' lesions and questionable fibrinoid changes were seen No proteinaceous material was seen in Bowman's spaces Many Bowman's capsules were

Diagnosis Chronic diffuse and generalized membranous glomerulonephritis, superimposed acute suppurative and chronic pyelonephritis

Case 29

R C (R&E 415795), a 34 year old housewife had migratory arthritis intermittent fever, and anorexia since 1949 For the next two years she suffered from pleuritic pain In August 1952 while vacationing in Florida she developed an erythematous rash of the face neck and elbows Lesions of lupus erythematosus were found in a section of a biopsy of skin and Hargraves s cells were seen on examination of the blood The following month swelling of the ankles appeared In May, 1954 she was admitted to hospital and found to have the nephrotic syndrome due to SLE The eyelids were puffy and there was much pretibial edema bilateral pleural effusions and ascites The liver was enlarged the blood pressure was 155/98 mm Hg but the optic fundi were normal The urine contained considerable protein and many hyaline granular fatty and erythrocyte casts Renal function was impaired The blood NPN was 69 mg/100 ml The serum albumin was 2 9 gm/100 ml and the serum cholesterol was 380 mg/100 ml Treatment with hydrocortisone resulted in clinical improvement and the edema subsided The dosage was reduced when he developed a toxic psychosis

In July she had recurrence of arthritis and pleuritic pain She complained of a diffuse alopecia of the scalp On admission to the University of Illinois Hospitals for study in September the blood pressure was 141/72 mm Hg and there was no edema There was much protein in the urine and leucocytes and many hyaline granular and fatty casts were seen in the sediment There was impairment of renal function A renal biopsy was done on September 28 Scaly erythematous lesions developed on the skin and regressed following treatment with chloroquin

In February 1955 she had a streptococcal pharyngitis and fever arthritis and pleurisy Penicillin was given and resulted in an improvement of her symptoms Two weeks later she was admitted for study The blood pressure was 130 84 mm Hg Urinalysis was unchanged The blood NPN was 45 mg/100 ml Later the liver and spleen became enlarged She was readmitted to hospital in June There was no peripheral edema The blood pressure was 160/90 mm Hg and grade II hypertensive retinopathy was found on funduscopic examination A third renal biopsy was done on June 21 Urinalysis was unchanged at this time

First Biopsy (June 1954) Adequate renal cortex (5 glomeruli) and very little medulla were included in the sections The glomeruli were markedly ischemic and somewhat lobulated There was distinct local hypercellularity due to endothelial cell proliferation and a local irregular thickening of the basement membrane in a few glomeruli In these same areas there was slight karyorrhexis but no hematoxylin bodies were seen There were numerous adhesions between the glomerular tufts and Bowman s capsules No epithelial crescents were noted Bowman s spaces contained a small amount of proteinaceous material and Bowman s capsules were slightly fibrotic The convoluted tubules were atrophic in places and their lining epithelium was moderately degenerated Their lumina contained small amounts of proteinaceous material The interstitial fibrous connective tissue was moderately increased and slightly edematous with moderate infiltration of chronic inflammatory cells There was mild thickening of the walls of the small arteries and changes suggestive but not diagnostic of fibrinoid degeneration were seen therein Mallory and PAS preparations confirmed these findings In Oil Red-O preparations of frozen sections a considerable amount of finely granular lipid material was noted within the cells of the convoluted tubules Gomori s preparations for alkaline phosphatase in frozen dried material disclosed the presence of very small amounts of the enzyme within the cells of the convoluted tubules

Diagnosis Late subacute local and generalized membranous and proliferative glomerulonephritis

Second Biopsy (September 1954) Adequate renal cortex (8 glomeruli) and medulla were included in the sections The glomeruli were ischemic and somewhat lobulated Partial hyalinization was seen in many due to fusion of thickened basement membranes



FIG 14 *Patient #23 Autopsy January 1956* Note the severe diffuse thickening of the glomerular basement membranes Fibrinoid changes and hyalinization are present in the glomerulus on the right Slight local hypercellularity is seen The tubules are atrophic and the interstitial connective tissue is fibrosed Elsewhere there was evidence of acute suppurative and chronic pyelonephritis (H&E × 340)

thick and fibrotic neither epithelial crescents nor glomerular adhesions were seen The interstitial fibrous connective tissue was markedly increased and slightly edematous and there was a diffuse infiltration of chronic inflammatory cells The tubules were markedly atrophic and contained occasional hyaline casts but little or no proteinaceous material The tubular epithelium was slightly degenerated The small arteries were slightly to moderately sclerotic In O l Red O preparations only minimal fatty degeneration of the tubular epithelium was noted

Diagnosis Early chronic diffuse membranous and local proliferative glomerulonephritis with superimposed interstitial nephritis

Autopsy (January 1956) (Fig 14) Many glomeruli were partially or completely hyalinized others were ischemic and lobulated There was a severe diffuse thickening of their basement membranes which in places appeared smudgy and granular suggestive of mild

aceous material hyaline casts and many polymorphonuclear leucocytes were found within the dilated tubules There were considerable degenerative changes of and abundant granular lipid was seen within the lining epithelium of the convoluted tubules There was fibrosis and

but no fibrinoid changes

and lympl nodes were enlarged The left wr st left elbow and left ankle were pa nf l red and s oll n Tl ere was 3+ pro e n n the urine and erythrocytes a few leucocy es and many hyal ne and granular casts in tl e s d ment The blood NPN was 34 mg/100 ml the serum cholesterol was 10? mg 100 ml the albumin was 3 0 gm/100 ml and the globulin was 3 0 gm/100 ml The serum sod um was 12? meq/L and the chlor de was 96 meq L The Wa ermann test was po ve Many Hargra es s cells were found on exam nat on of the per pheral bloo l Tl ere was x ray e dence of r ght pleural effu on SLE was d agnosed Sympto mat c mpro ement followed on treatment with 100 mg cort one d ly

On December 15 she became feverish and acutely ill and was readm tted to ho p tal The e was edema of the eyel ds and legs a macular face rash and enlargement of all the lymph nodes The bloo l pressure was 150 90 mm Hg B lateral pleural effus ons were found Tl ere was a ta hy a d a and ev dence of myocard t s on the electrocard ogram Protein many l ucocytes a few erythrocytes and many granular and hyal ne ca ts were found in the u ne The serum albm n was 2 6 gm/100 ml The hemoglob n was 8 4 gm/100 ml and the NPN was 49 mg 100 ml When treat d w th tetracycl ne and ncreased doses of o t one she mpro ed remarkably and be ame asymptomat c The do ge of cort sone was reduced to 75 mg da ly on d s l arge f om tl e hosp al One eek l er sl e was rea lm tted w h acute ab lom nal pa n an l anasar a The rash was st ll pre ent and the ret nal arter oles re in spasm The bloo l p essure was 190/100 mm Hg Tl e abdomen was r g d There was rebound ten lerness and hyperact ve bowel sounds The l er and lymph nodes we e enla ge l

There was g oss p o e nur a and g oss hematur a The ur nary spec fic gra tv as fixed at 1 010 Many leu ocytes and hyal ne gran lar and leucocyte casts and doubly refract le bod es were seen n the ur ne The blood NPN was 110 mg 100 ml R nal funct on was s erely mpa ed The serum album n was 1 7 gm/100 ml the serum chole terol was 135 mg 100 ml and the serum chol nesterase was 0 38 A pH un ts per hour Tl e Wassermann te t was negat e Many Harg aves s cells we e found on exam nat on of the bone marrow Tl e dosage of co t sone was ncreased to 75 mg day She became afebr e and the l ematuria ceas d The bloo l NPN fell to 47 mg 100 ml

On Jan ary 19 1955 a renal b opsy was done and subacute glomerulonephr t s was d gnosed *E col* was g own r peatedly from tl e urine but cultu e of the renal t s e was ster le Sl e as d s l arged f om tl e hosp tal and cont nued to take ort one at l ome How e e two weeks later on F bruary 7 she was re dm tted with pulmonary edema Tl e blood pres u e was 195 110 mm Hg the pulse as rap d and a gallop rythm was foun l S e was anem c an l was p s ng frank blood n the ur ne The bloo l NPN was 81 mg 100 ml Sl e was ac lot tl e serum potass u n was 7 5 meq I She exp r d n coma tl ree days later

Renal B opsy (Ja a y 1955) (F g 15) S ct ons nclude l a small fragment of renal co tex (6 glomer l) but no medulla The glomerul were is hem c some hat lob l ted and l yer cellul r Tl e e was a local rregular tl cken ng of tl e r basement membrane In some glomeru l part al hyal n zat on of the tuft was noted In places the th ckened basement membrane was sm dgy and granular strongly sugge t ng fibrino d In o l er glomerular tufts w e loop les ons ere seen Bowman s c psul s were th kened and fib o ed Ep thel al cell prol fe at on formed cre cents n Bowman s spaces wl cl conta ned a mo lera e amount of p ote naceo s n ate al There was cons derable at oply and deg ne a on of the l n ng ep hel m of the con ol te l tubules The r lum na conta ned much prote na eous mater al H al ne cas s were noted n a few of the collect ng t bules There was rather ma ked nterst t l fib os s w h some edema and considerable nfiltrat on of chron c nflam matory cell Sl gl t to mo lerate th cken ng and scleros s of tl e vall of the small arter es w s seen w l cl ang s gg t e of fib no d Mallory and PAS preparat ons confirmed the p esen e of fibr no d mater al n the glomeru l

Diagno s Late s ba te lo al an l g neral ze l p ol f at e a d men branous glome lo- neph tis

Autop y (Febru y 1955) (F gs 16 an l 17) The glom erul were moderately hypercellular lob l ted an l ischem c In man the tufts were compresse l by large fib o-ep tl el al

and obliteration of capillary lumina A few areas of hypercellularity were present There were many adhesions between the glomerular tufts and Bowman's capsules which were thickened and fibrosed A few "wire loop" lesions were seen, but no definite fibrinoid changes were detected within the glomeruli Neither epithelial crescents nor "hematoxylin" bodies were seen Marked atrophy and rather severe degenerative changes were seen in the lining epithelium of the convoluted tubules Their lumina contained a moderate amount of proteinaceous material There was a marked increase of the interstitial fibrous connective tissue which was slightly edematous and contained numerous areas of chronic inflammatory cells A few tubules contained hyaline casts Slight sclerosis and some fibrinoid changes were noted in the walls of the small arteries Mallory and PAS preparations confirmed these findings Comparison with the previous biopsy revealed a marked increase in the severity of the lesions Interstitial fibrosis and atrophy of the tubules was more marked and the fibrosis of the glomeruli had progressed

Diagnosis Chronic local and generalized membranous and proliferative glomerulonephritis superimposed interstitial nephritis

Third Biopsy (June, 1955) Adequate renal cortex (11 glomeruli) and medulla were included in the sections Some of the glomeruli were completely hyalinized In others there was a rather diffuse and severe thickening of the basement membrane and "wire loop" *lesions were seen There was little or no evidence of glomerular hypercellularity* Bowman's spaces were free of proteinaceous material and contained no epithelial crescents There was either moderate atrophy or some dilation of the convoluted tubules They contained a small amount of proteinaceous material and were lined by a slightly degenerated epithelium A few hyaline casts were noted in the collecting tubules The interstitial fibrous connective *tissue was moderately increased in areas and was infiltrated by chronic inflammatory cells* Slight to moderate sclerosis was noted in the walls of the small arteries but no definite fibrinoid changes were seen

Diagnosis Chronic local and generalized membranous glomerulonephritis

B PSEUDO-NEPHROTIC SYNDROME The four patients who died of SLE with lupus nephritis and the pseudonephrotic syndrome were all young women who were critically ill throughout their disease (Table VI) None of them lived longer than five months, and two (case #28 and M O) died within a few weeks of their first symptoms Two cases (#28 and 30) were treated with ACTH and cortisone, but to no avail One patient (case #28) died of myocarditis and renal disease The other three patients died in renal failure and uremia Oliguria was present, but none was anuric When first admitted to the hospital, all these patients were edematous and looked "nephrotic" They were pale, their faces were swollen, and their eyes were puffy It was, therefore, with some confidence that a clinical diagnosis of the nephrotic syndrome was made, and the finding of abnormally low serum cholesterol levels occasioned some surprise However, the other laboratory data—save for the low serum cholinesterase level in case #30—were consistent with what is usually found in the nephrotic state

Case 30

B S (R & E 424717), a 27 year old negro factory worker enjoyed good health until July 1954 when she had supraorbital headaches and was found to be anemic One month later



Fig 17 Patient #30 Autopsy February 1965 The glomerulus is adherent to Bowman's capsule in a few places Note the smudgy thickening of the glomerular basement membrane and a small area of karyorrhexis The vascular spaces around the glomerulus are congested (H&E × 340)

crescents In others there was irregular focal thickening of the basement membrane although no typical wire loop lesions were noted In a few smudgy granular fibrinoid changes were noted in the basement membrane In a few glomeruli considerable karyorrhexis was seen but no 'hematoxylin bodies were detected There was a moderate to severe interstitial fibrosis with considerable edema and infiltration of chronic inflammatory cells The convoluted tubules were either atrophic or dilated Their epithelium was low cuboidal and degenerated Their lumina contained proteinaceous material and occasional hyaline casts The small blood vessels were congested Occasional focal fibrinoid changes were noted in the slightly thickened walls of the small arteries Mallory and PAS preparations confirmed the presence of fibrinoid material in the glomeruli and in the walls of the arterioles Oil Red-O preparations disclosed the presence of fairly abundant granular lipid material in the epithelium of the convoluted tubules Comparison with the biopsy revealed some increase in the severity of the lesions particularly in the degeneration of the tubules

Diagnosis Late subacute diffuse and generalized proliferative and membranous glomerulonephritis

This case presents rather strikingly the severe involvement of the kidneys noted in the patients ill with the pseudo nephrotic syndrome and lupus nephritis The clinical state and course of the patients parallels in severity the degree of renal damage The type of lesions seen in these patients is also shown in Color Plate—Fig 9 (Case #32)

Assessment of the histologic analysis given in Table IV indicated that proliferative and basement membrane changes were not strikingly different in the nephrotic and pseudo nephrotic groups However with respect to 'hyaline' thrombi "wire loop lesions, karyorrhexis and the presence of hematoxylin"



FIG 15 *Patient #30 Biopsy January 1955* Note the epithelial and fibroepithelial crescents There is partial hyalinization of some glomeruli Some hypercellularity and irregular thickening of the glomerular basement membrane is also present Note the interstitial fibrosis and edema and the atrophy of the tubules in many areas (H&E × 200)

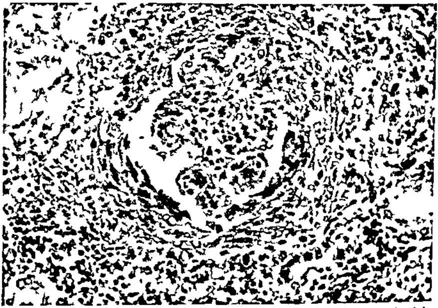


FIG 16 *Patient #30 Autopsy February 1955* Bowman's space is almost filled by a fibroepithelial crescent which completely surrounds the glomerulus The glomerular basement membrane is smudgy and irregularly thickened The periglomerular tissue is infiltrated by a large number of chronic inflammatory cells (H&E × 340)

TABLE VII

*An analysis of the nature and severity of the renal lesions in 40 abnormal biopsy and 9 autopsy specimens from 33 patients with SLE**

Histologic Features Analyzed	(A) Biopsies (40 specimens)					(B) Autopsies (9 specimens)				
	Grades of damage				Total number abnormal	Grades of damage				Total number abnormal
	4+	3+	2+	1+		4+	3+	2+	1+	
Glomeruli										
Basement membrane thickening	0	10	17	13	40	2	7	0	0	9
"Wire loop" lesions	0	3	10	16	29	0	3	4	2	9
Fibrinoid	0	1	8	21	30	1	2	3	2	8
Hypercellularity	1	4	9	15	29	0	3	3	3	9
Focal necrosis	0	1	2	10	13	0	0	0	5	5
Karyorrhexis	0	0	5	6	11	0	1	3	3	7
"Hematoxylin" bodies	0	0	2	2	4	0	2	1	0	3
"Hyaline" thrombi	0	0	0	0	0	0	2	0	1	3
Capsular adhesions	1	3	4	8	16	0	2	5	0	7
Crescents	0	0	3	0	3	0	1	2	0	3
Ischemia	0	13	7	18	38	0	4	4	1	9
Protein in Bowman's space	0	0	4	26	30	0	0	1	6	7
Total glomerular damage	1	12	16	11	40	6	2	1	0	9
Tubules										
Degeneration	0	6	15	16	37	0	8	1	0	9
Atrophy	2	1	7	12	22	1	1	0	5	7
Dilatation	1	0	15	8	24	0	0	3	1	4
Protein in tubular lumina	0	1	15	23	39	0	3	4	2	9
Casts in tubular lumina	0	3	6	14	23	0	2	3	3	8
Total tubular damage	1	10	9	16	36	2	5	2	0	9
Interstitial tissue										
Edema	0	3	7	9	19	0	3	2	4	9
Fibrosis	0	4	6	18	28	0	2	2	4	8
Inflammation	0	2	5	16	23	1	2	3	2	8
Arteries										
Sclerosis	0	0	5	20	25	0	0	3	3	6
Fibrinoid	0	0	4	13	17	0	1	2	3	6

* Cases studied clinically and pathologically

of the lesions enumerated above was graded from 0 (normal) to 4 plus (extremely severe and affecting all or almost all of the appropriate structures). The details of these analyses are set forth in Tables IV and VII.

(2) Terminology—

The pleomorphism and patchy character of the lesions of lupus nephritis made

bodies and fibrinoid degeneration the affection of the glomeruli was more common and more severe in the pseudo nephrotic group (Color Plate—Fig 9)

2 PATHOLOGIC MATERIAL

A Criteria for histologic analysis and definition of terms

In diffuse disorders of the kidneys such as diabetic glomerulosclerosis or proliferative glomerulonephritis it is unusual to find that all nephrons are affected by the disease process Many are spared and even in those nephrons that are involved the glomeruli are not damaged in a uniform manner The histologic picture is uneven and the lesions can be seen to be in different stages of development This was also found to be true for lupus nephritis In the early stage of the disease at least three glomeruli out of every five were seen to be damaged but they were not affected to the same degree As the disease progressed more and more glomeruli were involved and the lesion became more diffuse but still uneven in its development The irregularity of the process made careful evaluation of the sections most important lest the degree of damage be assessed incorrectly or erroneous interpretations arise For these reasons among others a fine systematic analysis was made of each biopsy or autopsy studied Details of the analysis and grading are given below In essence this was a semi quantitative histologic study which allowed us to reduce inherent errors to a minimum It permitted us to make a nice assessment of the type and degree of structural damage in each section it allowed us to compare—in detail—the findings in serial studies of the same patient and was to prove useful in comparing the degree of structural change with data from tests of renal function In this study of patients with lupus nephritis it was apparent that an adequate renal biopsy reflected accurately the type and degree of pathology in the kidneys In the nine cases which were studied both by biopsy and at postmortem excellent correlations were noted between the detailed analyses of the histology in the biopsy and in the autopsy specimens

(1) Methods of analysis—

On each specimen observations and assessments were made with respect to the following structures and pathologic entities Glomerular damage was assessed as a whole and the following glomerular structural changes were assessed individually thickening of the basement membrane increase in cellularity of the tuft (endothelial or epithelial) hyaline thrombi wire loop lesions karyorrhexis hematoxylin bodies fibrinoid changes in the glomerular basement membrane local necrotic lesions adhesions of the glomerulus to Bowman s capsule and fibroepithelial crescents The congestion or ischemia of the tuft were also evaluated Tubular damage was also assessed as a whole and the tubular changes observed and evaluated were degeneration atrophy, and dilatation The number of casts in the tubular lumina was also noted The presence of proteinaceous material was sought both in Bowman s spaces and in the tubular lumina In the interstitial tissue the changes evaluated were the presence of edema of fibrosis and of infiltration with inflammatory cells In the vessel walls sclerotic changes and fibrinoid degeneration were noted In each case the severity

TABLE VII

*An analysis of the nature and severity of the renal lesions in 40 abnormal biopsy and 9 autopsy specimens from 53 patients with SLE**

Histology Features Analyzed	(A) Biopsies (40 specimens)					(B) Autopsies (9 specimens)				
	Grades of damage				Total number abnormal	Grades of damage				Total number abnormal
	4+	3+	2+	1+		4+	3+	2+	1+	
Glomeruli										
Basement membrane thickening	0	10	17	13	40	2	7	0	0	9
Wire loop lesions	0	3	10	16	29	0	3	4	2	9
Fibrinoid	0	1	8	21	30	1	2	3	2	8
Hypercellularity	1	4	9	15	29	0	3	3	3	9
Local necrosis	0	1	2	10	13	0	0	0	5	5
Karyorrhexis	0	0	5	6	11	0	1	3	3	7
Hematoxylin bodies	0	0	2	2	4	0	2	1	0	3
Hyaline thrombi	0	0	0	0	0	0	2	0	1	3
Capsular adhesions	1	3	4	8	16	0	2	5	0	7
Crescents	0	0	3	0	3	0	1	2	0	3
Ischemia	0	13	7	18	38	0	4	4	1	9
Protein in Bowman's space	0	0	4	26	30	0	0	1	6	7
Total glomerular damage	1	12	16	11	40	6	2	1	0	9
Tubules										
Degeneration	0	6	15	16	37	0	8	1	0	9
Atrophy	2	1	7	12	22	1	1	0	5	7
Dilatation	1	0	15	8	24	0	0	3	1	4
Protein in tubular lumina	0	1	15	23	39	0	3	4	2	9
Casts in tubular lumina	0	3	6	14	23	0	2	3	3	[illegible]
Total tubular damage	1	10	9	16	36	2	5	2	0	[illegible]
Interstitial tissue										
Edema	0	3	7	9	19	0	3	2	4	[illegible]
Fibrosis	0	4	6	18	28	0	2	2	4	[illegible]
Inflammation	0	2	5	16	23	1	2	3	2	[illegible]
Arteries										
Sclerosis	0	0	5	20	25	0	0	3	3	
Fibrinoid	0	0	4	13	17	0	1	2	3	[illegible]

* Cases studied clinically and pathologically

of the lesions enumerated above was graded from 0 (normal) to 4 p
tremely severe and affecting all or almost all of the appropriate struct
details of these analyses are set forth in Tables IV and VII

(2) Terminology—

The pleomorphism and patchy character of the lesions of lupus nep

the selection of precise and descriptive diagnostic terms quite difficult Nonetheless in this study it was imperative to use accurate albeit cumbersome terminology

The following terms were chosen because they seemed to us to represent more accurately the character and degree of the histologic changes

Glomerulitis was used to indicate a proliferative and/or a membranous lesion of the glomerular tufts in the absence of any significant tubular damage or changes in the interstitial tissue

Glomerulonephritis was used to indicate a proliferative and/or a membranous lesion of the glomeruli associated with tubular and/or interstitial tissue changes

In both glomerulitis and glomerulonephritis the distribution and degree of lesions was specified by adding one or two of the following descriptive terms

1) *Local* referring to a glomerulitis or glomerulonephritis characterized by lesions affecting one or more areas within each glomerulus

2) *Diffuse* referring to lesions affecting diffusely each involved glomerulus

3) *Focal* referring to lesions either local or diffuse affecting only some glomeruli

4) *Generalized* referring to lesions either local or diffuse affecting all or almost all glomeruli

(3) Material—

In the present study are included 57 biopsy and nine autopsy specimens from 33 patients The detailed histologic analysis for each specimen from each patient is set out in Table IV A summary of the histologic findings is set forth in Table VII A and B

The slides from 21 cases of SLE in the files of the Pathology Departments have also been reviewed and the same methods of analysis described above were used to study them (Table IX) In addition 15 autopsy cases of glomerulonephritis were studied by the same methods (Table X) These analyses were compared with those from patients with lupus nephritis (Table XI)

B The renal lesions in cases studied by biopsy

(1) The glomerular lesions—

Thickening of the glomerular basement membrane The glomerular basement membrane is normally a thin delicate eosinophilic structure which is colored purplish red with the PAS technique and blue with the aniline blue of the Mal

known that the thickness of the basement membrane may vary within a ... range in perfectly normal glomeruli This is probably the result of distention or retraction of the basement membrane resulting from congestion or ischemia of the glomerular tuft and was taken into account before establishing the degree of basement membrane thickening especially in the early stage of lupus nephritis

Thickening of the glomerular basement membrane was present in all 40 ab



Fig 18 *Patient #17 Second Biopsy May 1955* Note the local thickening of the glomerular basement membrane especially at the periphery of the glomerular tuft The smudgy appearance of the thickening is suggestive of fibrinoid change In the areas of thickening note the slight but definite hypercellularity due to clumping and/or proliferation of endothelial cells (H&E × 500)

normal biopsy and in all nine autopsy specimens It was more severe in the autopsy specimens as might be expected The thickening of the basement membrane was *usually local rather than diffuse the peripheral portions of the glomerular tuft* being more commonly affected (Fig 18) When present at least 50 per cent of the glomeruli were usually affected A diffuse regular thickening of the glomerular basement membrane similar to that seen in membranous glomerulonephritis was observed only very late in the disease The severity of the thickening varied considerably in different areas of the same glomerulus (Fig 19) and from one glomerulus to another As it increased around various capillary loops the capillary lumen proportionately decreased in size and contained fewer red blood cells In some cases the capillary lumina became completely obliterated in patches (Fig 20) No evaluation of basement membrane thickening was made when the glomeruli were partially or completely hyalinized Complete hyalinization was most unusual and was seen only twice (Fig 21)

Wire loop lesions were seen in 29 biopsy and all nine autopsy specimens *The incidence and severity of wire loop lesions was greater in the autopsy* material These lesions were usually not observed unless the thickening of the glomerular basement membrane was at least of moderate severity (2+ or greater) The involved capillary loops appeared stiff and rigid (Fig 22) Early in the disease they were seen in the peripheral portion of the glomeruli, later,

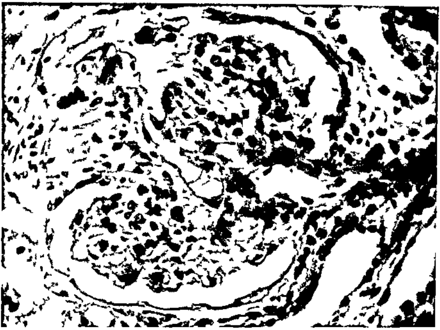


FIG 19 *Patient #22 Second Biopsy June 1955* Note a fairly diffuse but irregular thickening of the glomerular basement membrane and narrowing of the capillary lumina Note also on the left the well organized adhesion between the glomerular tuft and Bowman's capsule (H&E × 480)

although they were more common at the periphery, they were seen in some cases throughout the glomerular tuft Slight to moderate fibrinoid changes were found in all but four of the sections in which "wire loop" lesions were seen

Fibrinoid changes The presence of fibrinoid changes in the glomerular basement membrane and in the walls of the small arteries was recognized or at least suspected by the smudgy granular strongly eosinophilic appearance of the involved structures in H&E stained sections (Color Plate—Fig 2 and 5) The affected areas appeared more irregular and less dense or "stiff" than comparable lesions resulting from hyaline or amyloid deposition Confirmation of the fibrinoid change was obtained in Mallory preparations in which the involved basement membrane stained a reddish color contrasting with the blue of the uninvolved connective tissue (Color Plate—Fig 10) In the PAS preparations fibrinoid stained a particularly intense red purple color With milder changes (+) the special staining reactions were not as specific Fibrinoid changes were found more commonly in the glomeruli than in the small arteries and arterioles and were seen in 30 biopsy and in eight autopsy specimens

Proliferative changes in the glomerular tuft Varying degrees of hypercellularity were noted in 29 biopsy and nine autopsy specimens Evaluation of proliferative changes presented considerable difficulty especially in the early stages of the disease when the degree of hypercellularity was slight Sections cut above or below 5 microns—the section thickness used consistently in this study—may

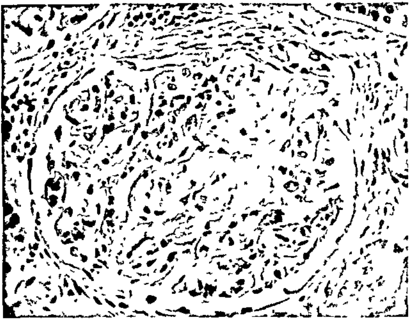


Fig 20 *Patient #25 Autopsy May 1955* Note in one area that the thickening of the glomerular basement membrane is severe there is complete obliteration of the capillaries and early hyalinization Elsewhere in the glomerulus the basement membrane is only moderately thickened (H&E × 500)

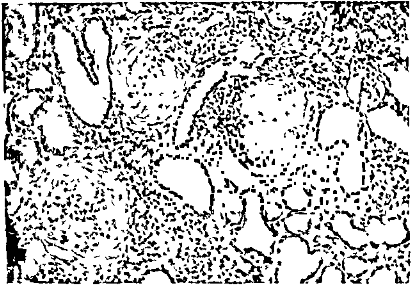


Fig 21 *Patient #33 Biopsy, July 1955* Partial and complete hyalinization of glomeruli in advanced lupus nephritis In the glomerulus at the left severe diffuse basement membrane thickening can still be recognized This degree of hyalinization of glomeruli is unusual even in advanced lupus nephritis (H&E × 250)



FIG 22 *Patient #9 Biopsy June 1955* Note the diffuse but irregular thickening of the glomerular basement membrane Distinct wire loops can be seen especially at the periphery of the glomerular tuft Note that the involved capillary loops appear stiff and slightly smudgy (H&E × 400)

lead to over or under evaluation of the degree of glomerular cellularity When hypercellularity was present in the milder lesions it was almost exclusively noted in the peripheral portion of the glomerular tuft (Color Plate—Fig 1) as it increased in severity it tended to become more diffuse (Fig 23) and was often associated with varying degrees of glomerular lobulation Local thickening of the basement membrane or fibrinoid changes or both were observed frequently in the areas of hypercellularity In almost all cases the increased number of cells in the glomerular tufts appeared to be due to endothelial rather than epithelial proliferation It was only in the more advanced stages of lupus nephritis that epithelial cells appeared to have increased in number either in the visceral or in the parietal layer of the glomerulus Reduction in the size of glomerular capillaries due to hyaline or fibrinoid changes led to a conglutination and apparent increase of endothelial cells in some areas This was taken into account before determining the degree of hypercellularity

Local necrosis of the glomerular tuft A small local area of necrosis in the peripheral portion of the glomerulus was one of the lesions considered strongly suggestive and almost pathognomonic of lupus nephritis (Color Plate Fig 2 and Fig 38 and 40) This lesion was seen in one or more glomeruli in 13 biopsy and five autopsy specimens It was characterized by local areas of basement membrane thickening with obliteration of capillaries fibrinoid changes and early necrosis a few lymphocytes and occasionally polymorphonuclear leuko

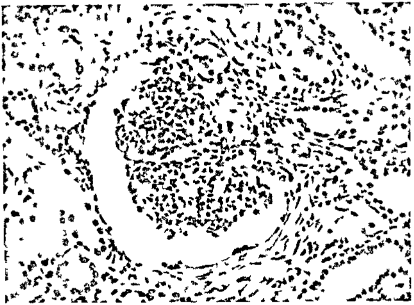


Fig 23 *Patient #[illegible] Biopsy June 195[illegible]* Note the marked hypercellularity of the glomerulus due to proliferation of the endothelial cells The basement membrane thickening is mild and is obscured except in a few areas by the cellular proliferation This type of diffuse glomerulitis is not common in lupus nephritis (H&E × 370)

cytes were seen Karyorrhexis of endothelial epithelial and inflammatory cells was an almost constant feature of the lesion and hematoxylin bodies were observed in about one third of them These local necrotic lesions resembled closely those which occur in embolic glomerulonephritis of Lohlein By contrast with embolic glomerulonephritis necrosis was not as prominent inflammatory cells were less numerous and micro organisms were never observed even in sections especially prepared to demonstrate bacteria Karyorrhexis was common to both embolic glomerulonephritis and lupus nephritis but the presence of hematoxylin bodies was considered quite characteristic for lupus nephritis The nature of the local and focal glomerular necrosis in lupus nephritis is not well understood

Hematoxylin bodies were observed in only four biopsy and three autopsy specimens They were found only within the glomeruli in association invariably with karyorrhexis and usually with fibrinoid changes (Color Plate—Fig 9 and Fig 40) They were rounded or oval structures of approximately nuclear size or smaller they stained dark lavender to purplish red with hematoxylin in contrast with the blue black color of the nuclei Additional stains used for the identification of hematoxylin bodies included iron hematoxylin (black) and pyronine (purple red) These special staining reactions were not found to be essential for their identification

Hyaline thrombi which occluded the lumina of the glomerular capillaries

were observed in three autopsy specimens and were not seen in the biopsy specimens They were rounded or elongated cylindrical structures homogeneous and strongly eosinophilic (Color Plate—Fig 9 and 10) They filled more or less completely the lumina of the capillaries and frequently were attached to the capillary wall These thrombi reacted in a strongly positive manner in PAS preparations and stained red in Mallory Azan preparations No red blood cells were seen within them nor were they thought to participate in their constitution The staining properties and general appearance of hyaline thrombi made differentiation from superficially similar capillary lesions such as those observed in diabetic glomerulosclerosis quite easy The material constituting hyaline thrombi although not exactly identified histochemically, was certainly more closely related to fibrin or fibrinoid than to hyaline It appears to us that in this context the term hyaline should be abandoned in favor of fibrin or fibrinoid

Capsular adhesions Adhesions between the glomerular tufts and Bowman s capsules were observed in 16 biopsy and in seven autopsy specimens In the early stage of their development thin strands of smudgy or smooth hyaline material were seen As these synechiae became larger they involved progressively larger areas of the surface of the glomerular tuft and eventually formed well developed fibrous adhesions (Color Plate—Fig 3) Frequently the process was accompanied by a certain degree of retraction and distortion of the glomerulus Adhesions developed particularly in relation to areas of local hypercellularity or necrosis of the glomerular tuft (Fig 39 and 40)—evidently as a result of inflammatory alterations at the periphery of the glomerulus

Fibro epithelial crescents were noted in three biopsy and in three autopsy specimens (Color Plate—Fig 6 and Fig 15 and 16) They were always associated with capsular adhesions They did not differ significantly from the fibro epithelial crescents seen in the common variety of subacute glomerulonephritis

Glomerular ischemia The number of red blood cells present in the capillaries of the glomerular tuft was evaluated Our criteria in this evaluation were based on our experience of approximately fifty biopsy specimens of essentially normal kidneys Grades from 0 to 4+ indicate progressively severe degrees of glomerular ischemia It was seen in 38 abnormal biopsy specimens and in nine autopsy specimens The presence of ischemia was thought to be significant only when associated with other lesions of the glomerulus

Overall glomerular damage After each element in the glomerulus had been analyzed independently an estimate of total glomerular damage was made The degree of glomerular damage was graded in the usual manner taking into consideration not only the severity of the lesions but also the proportion of affected glomeruli Various degrees of glomerular damage were found in 40 biopsy and in nine autopsy specimens As expected the incidence and severity of the glomerular lesions was greater in the autopsy specimens

(2) Tubular lesions—

The state of the renal tubules was also evaluated As in many renal diseases the changes observed in the tubules in the various stages of lupus nephritis were

not specific An accurate analysis was made only of the changes seen in the proximal and distal convoluted tubules since renal medulla was present in approximately fifty per cent of the biopsies In biopsy material the appearance of the tubular epithelium, even in the normal kidney was different from that usually seen postmortem As a rule in biopsy specimens the free margin of the epithelial cells was more irregular and there was greater variation in the height of the cells As a result the size of the tubular lumen also varied The cause of the irregularity of the free margin is not known It may be the result of the trauma of the biopsy needle Another possible explanation is that it is due to the varying activity of the cell and represents absorption of protein and solutes The varying height of the epithelium may represent varying states of diuresis (28 135 181) These features peculiar to biopsy material made the evaluation of tubular damage more difficult

Degeneration of the tubular epithelium was found in 37 biopsy and nine autopsy specimens Various features were taken into consideration The following features were commonly found swelling of the cells with or without vacuolization of their cytoplasm and an excessive irregularity and fraying of the free margin of the cells with loss of the brush border (Fig 39 and 40) In a few cases in which Oil-Red O preparations for lipids were made vacuolization was seen to be due to fat droplets Occasionally finely divided lipid material was observed in tubular cells in which vacuolization was not evident in H&E preparations At times the cytoplasm of the tubular cells contained eosinophilic 'hyaline' granules These rarely gave a strongly positive reaction in PAS preparations These granules may represent the results of tubular protein reabsorption (210 211) In a few cases the Gomori technique was used to stain alkaline phosphatase in the tubules It appeared to us that the concentration of this enzyme was decreased proportionately to the degree of tubular degeneration Evaluation of this feature was difficult because of the lack of a sufficient number of normal control biopsy specimens and because of the observation that even in normals there was a considerable variation in the concentration of alkaline phosphatase in the tubular cells

Atrophy of the convoluted tubules was judged by the reduction in the size of the tubules and in the number and size of their cellular components Pyknosis of nuclei was frequently associated with cellular atrophy As a rule the tubular basement membrane was thickened in those cases in which atrophy was severe Tubular atrophy was observed in 22 biopsy and seven autopsy specimens (Fig 12 14 and 15)

Dilatation of tubules was observed in 24 biopsy and in four autopsy specimens As a rule dilatation was found only in some groups of nephrons while others were atrophied (Fig 8 and 21) It never reached the proportions seen so commonly in chronic renal disease particularly pyelonephritis

Proteinaceous material was present in Bowman's spaces (Fig 40) and in the lumina of the convoluted tubules in varying amounts even in renal tissue from patients whose urine was free of significant amounts of protein At times the eosinophilic amorphous or granular proteinaceous material appeared to be in

direct continuity with the irregular free border of the tubules and with the cytoplasm of the epithelial cells of Bowman's capsule and of the tubules. However in many cases the protein precipitate appeared to be free in the lumen and its amount was roughly proportional to the degree of proteinuria (see also Table XIII).

Casts. The casts seen within the tubules were usually hyaline, less commonly granular and infrequently cellular in type. Erythrocyte casts were seen in only one case (#23). As a rule the casts stained a deep red purple color with PAS. *Occasionally they were quite large and had a waxy appearance.* They seemed to be more numerous in the collecting tubules. Occasionally casts were observed in biopsy specimens which were otherwise entirely normal.

Overall tubular damage. The estimate of total tubular damage was made after the above features were analyzed. The tubules were damaged in varying degrees in 36 biopsy and nine autopsy specimens and were significantly more severe in the latter.

(3) Interstitial tissue—

The appearance of the interstitial tissue received considerable attention. It is in our opinion *the forgotten tissue component of the kidneys* and abnormalities therein may have greater functional significance than is generally thought (5, 89). The three basic abnormalities observed in the interstitial fibrous connective tissue were edema, fibrosis and inflammation. Edema was found in 19 biopsy and in all nine autopsy specimens. It was characterized by a swelling of the connective tissue with resulting separation of fibrillar and cellular elements and often a change in staining qualities. The normal eosinophilia was usually decreased and in patchy areas of several biopsies a pale gray blue color was noted, suggestive of alterations in the mucopolysaccharides of the ground substance (Color Plate—Fig 6). In general edema was noted in the relatively early stages of lupus nephritis and reached its maximum in the subacute stage of the disease (Fig 8). Varying degrees of fibrosis were noted in 28 biopsy and in eight autopsy specimens. The degree of fibrosis was related to the chronicity of the disease. As the disease process became more chronic a greater density and occasionally hyalinization of the fibrous connective tissue was observed (Fig 12 and 14). PAS and Mallory preparations were useful in evaluating these changes more accurately. *When present both interstitial edema and fibrosis* were patchy in distribution, especially in the cortex, and as a rule were seen in areas where the glomeruli were more severely damaged.

Interstitial infiltration of inflammatory cells was noted usually in the moderately advanced or advanced stages of the disease and was found in 23 biopsy and eight autopsy specimens. It was characterized by relatively small numbers of lymphocytes, plasma cells and histiocytes located, as a rule, in the areas of fibrosis and edema (Fig 8). Perivascular distribution of interstitial edema, fibrosis and inflammatory cells was not a striking feature. Occasionally large infiltrates were observed which were often periglomerular, especially when acute lesions were present in the glomeruli (Fig 16). In a few cases a superimposed infection was suggested by *the large number and distribution of in-*

flammatory cells and by the presence of neutrophils and eosinophils This interpretation was reinforced on occasion by positive bacterial cultures obtained from renal tissue at the time of biopsy Neither definite fibrinoid changes nor 'hematoxylin bodies were observed in the interstitial fibrous connective tissue

(4) Vessels—

As a rule a few small arteries and arterioles could be recognized in each biopsy specimen In general the vascular changes were not impressive The most common arterial lesion was fibrosis of the wall with or without hyalinization and mild narrowing of the lumen Sclerosis of the vessel wall was present in 25 biopsy and six autopsy specimens A significant degree of vascular sclerosis was seen only in the more advanced and chronic stages of lupus nephritis Fibrinoid changes in the vessels were carefully searched for and were observed in 17 biopsy and six autopsy specimens However they were of significant degree (2+ or 3+) in only four biopsy and three autopsy specimens (Fig 24) The presence of fibrinoid in these cases was confirmed by the staining properties of this material in PAS and Mallory preparations In general fibrinoid was less commonly observed in the walls of small arteries and arterioles than in the glomeruli

C The character and distribution of renal lesions

When the detailed analysis was completed a pathologic diagnosis was made for each biopsy and each autopsy specimen using the descriptive terminology

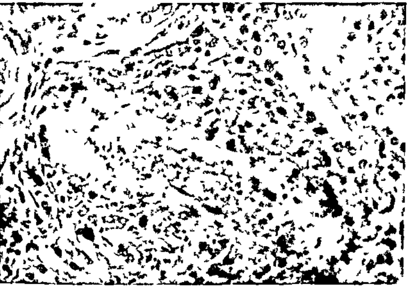


FIG 24 *Case of SLE from postmortem series* (R&L Autopsy 135/1950) Small renal artery Note severe fibrinoid changes involving most of the vessel wall There are a few inflammatory cells in the periarterial tissues (H&E × 330)

TABLE VIII

The type and distribution of the renal lesions in lupus nephritis in 40 abnormal biopsy and 9 autopsy specimens

Histology of Lupus Nephritis	Glomerulitis	Glomerulonephritis	
	15 biopsy and no (0) autopsy specimens	25 biopsy specimens	9 autopsy specimens
1 Type of lesion			
(a) Membranous	6	9	2
(b) Proliferative and membranous	6	3	0
(c) Membranous and proliferative	3	12	7
(d) Subacute	0	4	3
(e) Chronic	0	6	2
2 Distribution of lesions in glomerulus			
(a) Local	15	20	5
(b) Diffuse	0	5	4
3 Distribution of lesions throughout section			
(a) Focal	5	3	0
(b) Generalized	10	22	9

defined above In Table VIII are grouped the various diagnoses according to the character and distribution of the lesions Glomerulitis was found in 15 biopsy specimens but was not seen in any autopsy specimen The lesions within each glomerulus were local in all cases with glomerulitis, and in most of those with glomerulonephritis Diffuse lesions were noted late in the course of the disease only in five biopsy and four autopsy specimens Focal lesions affecting a few glomeruli were found only in five sections with glomerulitis and in three with glomerulonephritis Thus in the majority of cases the lesions affected all or almost all the glomeruli—even when the renal lesions were in an early stage

In all abnormal sections examined glomerular basement membrane thickening was seen Associated proliferative changes were noted in 25 biopsy and seven autopsy specimens Proliferative changes were slightly more predominant among the biopsies with glomerulitis, changes in the basement membrane predominated among the biopsy and autopsy specimens with glomerulonephritis

In 15 of the 34 specimens diagnosed as lupus glomerulonephritis the histologic picture was either subacute (seven cases) or chronic lupus glomerulonephritis (eight cases) The histopathologic criteria used to diagnose the subacute and chronic glomerulonephritic stages of lupus nephritis were not significantly different from those used to diagnose the common types of subacute and chronic glomerulonephritis In the subacute stage, however, the glomerular changes of *lupus nephritis* were still prominent in most cases In the chronic stage the changes were less suggestive of lupus nephritis, and in some cases the changes of lupus nephritis could not be recognized

When the histologic findings were analyzed for severity and type of lesions no differences were noted with age, sex, or race No relationship was noted between the duration of symptoms and signs of SLE and the severity of the

renal lesions However, once the renal lesion was established it was progressive in most instances

D The renal lesions in cases of SLE studied postmortem

In order further to evaluate the findings in the renal biopsies the kidneys of 21 autopsy cases from the files of the Departments of Pathology were studied These cases were selected because they had had the characteristic clinical features of SLE during life, and because there was pathologic evidence of SLE in organs other than the kidneys The findings are set out in Table IX Many

TABLE IX

*An analysis of the nature and severity of the renal lesions in 20 autopsy specimens from patients with SLE**

Histologic Features Analyzed	Grades of Damage				Total Number Abnormal
	4+	3+	2+	1+	
Glomeruli					
Basement membrane thickening	2	7	6	5	20
"Wire loop" lesions	1	3	3	5	12
Fibrinoid	1	2	4	2	[illegible]
Hypercellularity	2	1	6	9	19
Focal necrosis	0	0	4	2	6
Karyorrhexis	0	0	3	4	7
"Hematoxylin" bodies	0	0	0	5	5
"Hyaline" thrombi	1	0	2	3	6
Capsular adhesions	1	2	2	6	11
Crescents	2	0	2	4	8
Ischemia	0	9	8	2	19
Protein in Bowman's space	0	0	2	5	7
Total glomerular damage	4	8	4	4	20
Tubules					
Degeneration	0	6	8	4	18
Atrophy	0	0	1	12	13
Dilatation	0	0	3	8	11
Protein in tubular lumina	1	1	11	7	20
Casts in tubular lumina	0	2	3	8	13
Total tubular damage	1	5	10	4	20
Interstitial tissue					
Edema	0	1	4	10	15
Fibrosis	0	0	2	13	15
Inflammation	0	3	3	10	16
Arteries					
Sclerosis	0	0	1	10	11
Fibrinoid	0	2	2	1	5

* Cases studied from the files of the Departments of Pathology 1943 1956

of the cases in this group had died with clinical evidence of severe renal involvement

It is apparent (Tables VII IX and XI) that the incidence and severity of the renal lesions was considerably greater in the autopsy than in the biopsy specimens This was true of almost all features analyzed Lesions such as hematoxylin bodies and hyaline thrombi were definitely more common in the autopsy than in the biopsy specimens *This may perhaps be explained by* the fact that a far larger number of glomeruli was available for study in autopsy slides On the other hand lesions such as local necrosis were only slightly more frequent in autopsy specimens

In one instance the kidney was histologically normal Seven had lupus glomerulitis and thirteen were diagnosed as lupus glomerulonephritis Of the latter group seven had subacute lupus glomerulonephritis and in no case was chronic lupus glomerulonephritis found Basement membrane changes and cellular proliferation were noted in 12 cases changes in the basement membrane without proliferative changes were seen in eight As was expected the histo



FIG 25 (a) *Patient #30 Autopsy February 1955* Portion of external surface of a kidney in severe subacute lupus glomerulonephritis The capsule has been removed Note the swollen appearance and the distinct mottling of the organ A few punctate hemorrhages can be seen



Fig 25 (b) *Patient #30 Autopsy February 1955* Section through the same kidney Note the mottling of the swollen cortex The corticomedullary junction is indistinct

logic abnormalities in the kidneys had progressed to an advanced stage in a large proportion of those who had died

Grossly the kidneys were heavier than normal and appeared swollen pale and mottled (Fig 25) A mild contraction of the kidney was seen in very few specimens (Fig 26) This is in agreement with the experience of other investigators who have remarked on the rarity of contraction of the kidneys in SLE Ten of the 21 autopsies were done between 1943 and 1950 the remainder from 1951 to 1956 The lesions were distinctly more severe in the later group This may be related to prolongation of life due to treatment of patients with ACTH and steroid hormones A separate comparison was also made between the nine autopsy specimens from cases clinically studied and treated by us and the 11 autopsy specimens from patients who died between 1951 and 1956 and who were not studied clinically by us The incidence and severity of the renal lesions was somewhat more severe in the group studied by us Our patients were studied more closely were treated more intensively and lived longer than the 11 pa

F



Fig 26 Patient#93 Autopsy January 1956 Chronic lupus glomerulonephritis and superimposed pyelonephritis Section of kidney Note that the cortex is narrow The radiating pattern of the pyramids is abnormally prominent Small interstitial abscesses can be seen at the upper and lower poles

tients in the post mortem group 1951 1956 Therefore the increased severity of the renal lesions in the group of patients studied by us may be related to prolongation of life

E The renal lesions in cases of subacute glomerulonephritis studied postmortem

Because of the morphologic resemblance of the lesions of the advanced stages of lupus nephritis to those of the common type of glomerulonephritis a comparative analysis was made of the histologic features in the two diseases In Table X are set out the histologic findings in the kidneys of 15 autopsy cases of subacute glomerulonephritis These were consecutive cases in the period 1952–1955 taken from the files of the Department of Pathology in all the clinical and pathologic features were considered to be typical of subacute glomerulonephritis *and in none was there clinical or pathologic evidence of SLE*

A comparison of these findings (Table X) with those of the autopsy cases of lupus nephritis (Tables VII and IX) revealed that although many features were common to both diseases there were also many differences (Table XI) Certain features considered characteristic of lupus nephritis such as local necrosis karyorrhexis hematoxylin bodies and hyaline thrombi did not occur or were very rarely seen in subacute glomerulonephritis Wire loop lesions and fibrinoid degeneration were far less commonly found than in lupus nephritis *Mild degrees of glomerular hypercellularity* were common in lupus nephritis but

TABLE X

*An analysis of the nature and severity of the renal lesions in 15 autopsy specimens from patients with subacute glomerulonephritis**

Histologic Features Analyzed	Grades of Damage				Total Number Abnormal
	4+	3+	2+	1+	
Glomeruli					
Basement membrane thickening	1	3	1	6	11
'Wire loop' lesions	0	0	1	2	3
Fibrinoid	0	1	0	1	2
Hypercellularity	2	10	1	2	15
Focal necrosis	0	0	1	0	1
Karyorrhexis	0	0	1	0	1
'Hematoxylin' bodies	0	0	0	0	0
'Hyaline' thrombi	0	0	0	1	1
Capsular adhesions	5	5	2	3	15
Crescents	4	5	1	0	10
Ischemia	0	10	2	3	15
Protein in Bowman's space	0	0	1	3	4
Total glomerular damage	8	4	3	0	15
Tubules					
Degeneration	0	15	0	0	15
Atrophy	0	3	8	3	14
Dilatation	0	3	4	5	12
Protein in tubular lumina	0	7	7	1	15
Casts in tubular lumina	0	3	10	1	14
Total tubular damage	2	13	0	0	15
Interstitial tissue					
Edema	0	1	5	9	15
Fibrosis	0	3	10	2	15
Inflammation	0	2	9	3	14
Arteries					
Sclerosis	0	0	0	9	9
Fibrinoid	0	0	0	1	1

* Cases studied from the files of the Department of Pathology, University of Illinois, 1952 1955

the incidence and severity of this feature were definitely greater in subacute glomerulonephritis. Fibroepithelial crescents and glomerulocapsular adhesions were more common in subacute glomerulonephritis.

Tubular damage was definitely more severe in subacute glomerulonephritis. This was especially true of atrophy and dilatation, and pointed to a more chronic disease process. This interpretation was confirmed by the higher incidence and greater severity of interstitial fibrosis among the cases of subacute glomerulo-

TABLE XI

A comparison of the incidence of histologic abnormalities in biopsy and autopsy specimens of lupus nephritis, with autopsy specimens of glomerulonephritis

Histologic Features Analyzed	Percentage Incidence of Abnormalities in			
	Lupus nephritis			Glomerulonephritis
	40 biopsy specimens*	9 autopsy specimens†	20 autopsy specimens‡	15 autopsy specimens§
Glomeruli				
Basement membrane thickening	100	100	100	73
"Wire loop" lesions	74	100	60	20
Fibrinoid	77	89	45	13
Hypercellularity	74	100	90	100
Local necrosis	34	56	30	7
Karyorrhexis	28	78	35	7
"Hematoxylin" bodies	10	33	25	0
"Hyaline" thrombi	0	33	30	7
Capsular adhesions	41	78	55	100
Crescents	8	33	40	67
Ischemia	95	100	95	100
Protein in Bowman's space	75	78	35	27
Tubules				
Degeneration	93	100	90	100
Atrophy	56	78	65	93
Dilatation	60	44	55	80
Protein in tubular lumina	97	100	100	100
Casts in tubular lumina	58	89	65	93
Interstitial tissue				
Edema	49	100	75	100
Fibrosis	70	89	75	100
Inflammation	58	89	80	93
Arteries				
Sclerosis	63	67	55	60
Fibrinoid	44	67	25	7

* See Table VII A
† See Table VII B
‡ See Table IX
§ See Table X

nephritis. Fibrinoid changes in the arteries were definitely more common in the cases with lupus nephritis, while the incidence of sclerotic changes was similar in the two series.

F. Evolution of the renal lesions of lupus nephritis

(1) Analysis of the findings—

In 21 patients two or more specimens were studied by biopsy or autopsy at intervals varying between six weeks and sixteen months. Seven of these patients died, and the analysis of their autopsy studies is included in this discussion.

In most cases the interval between studies was four to eight months. Two specimens were studied from each of twelve patients, three specimens from each of seven patients, and four and five specimens from one patient each. The shortest period between the first and last histologic study was six weeks (#27), the longest was 23 months (#31).

The first biopsy was normal in six patients. In four (#3, 5, 7, 8) the second or third biopsies taken at intervals up to 22 months remained normal. In the other two (#6, 11) repeat studies disclosed the development of a mild to moderate membranous glomerulonephritis in four and fourteen months respectively. Glomerulitis was found in the first biopsy of seven patients. In one (#16) the lesion was unchanged one year later. Slight progression of the lesion occurred in two patients (#12, 14) in fifteen and four months respectively. In four cases (#13, 18, 19, 21) the lesion progressed from glomerulitis to glomerulonephritis during a period of observation ranging from four to ten months.

Glomerulonephritis was observed in the first biopsy in eight instances. In one (#29) there was slight progression in the first three months but subsequently the changes had not progressed nine months later.[6] In seven (#22, 23, 25, 26, 27, 30, 31) considerable progression of the already severe renal lesion was observed in a period ranging from 6 weeks to 23 months.

(2) Reconstruction of the histologic evolution of lupus nephritis.—

From our studies it is evident that the renal lesions of lupus nephritis, once they had developed, inevitably progressed; the morphologic appearance of the lesion changed with this progression. The serial pathologic specimens available in this study have permitted an accurate reconstruction of the histologic evolution of lupus nephritis from the earliest to the most advanced stages.

The earliest and milder lesions of lupus nephritis were confined to the glomeruli. At this stage an irregular focal thickening of the basement membrane in small areas at the periphery of the tuft was frequently found. It has a somewhat smudgy appearence. Although strongly suggestive of fibrinoid this appearence could not definitely be attributed to deposition of fibrinoid as the PAS and Mallory stains did not usually give the characteristic staining reactions. In almost all instances a mild focal proliferation of endothelial cells was noted in association with the thickening of the basement membrane. This usually appeared to be due in part, at least, to clumping of cells, the result of narrowing and of conglutination of capillary loops. In some cases a diffuse proliferative glomerulitis was noted. This suggested that the areas of focal hypercellularity were not due only to clumping of cells but that there was true focal proliferation of endothelial cells. The importance of these early glomerular lesions of lupus nephritis has not been emphasized except by Stickney and Keith (272, 274) and in Smith's recent study (264). Moreover they have detected and we have confirmed that these lesions are present in autopsy specimens side by side with more advanced and typical changes. They probably represent glomeruli recently affected in a fresh exacerbation of S.L.E.

[6]This patient has since been restudied twelve months later. No further progression of the renal lesion has occurred.

Some cases of glomerulitis progressed slowly during the period of observation In many cases the local and focal glomerulitis progressed gradually and th following features more peculiar to lupus nephritis appeared the narrowin and conglutination of capillary loops became more marked in local areas unti the local necrotic lesions developed within these lesions karyorrhexis hema toxylin bodies fibrinoid changes and occasional hyaline thrombi were ob served In other cases the local hypercellularity was less obvious as thickening and fibrinoid changes of the glomerular basement membrane became the pre dominant feature At first this was observed at the periphery of the glomerulus *later areas throughout the glomerulus were involved Wire loop lesions were* noted at this stage This was the membranous form of lupus nephritis which was found either alone or in combination with local necrosis

Frequently in the areas of local necrosis the glomerulus became adherent to Bowman s capsule The e local adhesions gradually underwent organization and eventually became fibrosed When adhesions between the altered glomerular tuft and Bowman s capsule were more extensive proliferation of epithelial cells was observed and epithelial crescents and later fibroepithelial crescents were formed At this stage which we have called subacute lupus glomerulonephritis the histologic features peculiar to lupus nephritis were less prominent in some cases but were still present Evolution to chronic glmorulonephritis with fi brosis and hyalinization of many glomeruli was uncommon in both biopsy and autopsy specimens

In the early stages no tubular vascular or interstitial tissue changes were observed As the glomerular lesions became more pronounced tubular degenera tive changes appeared the interstitial tissue became edematous at first in focal areas and later throughout the sections Interstitial fibrosis was observed later than interstitial edema in the course of the disease *Small interstitial infiltrates* of chronic inflammatory cells began to appear with the development of inter stitial edema and fibrosis Initially foci of inflammatory cells were often located around the glomeruli only later were they observed in other areas of the cortex and medulla A superimposed pyelonephritis was observed in the subacute and chronic glomerulonephritic stages in three instances Vascular changes occurred only late in the disease Fibrinoid changes were observed in the walls of small arteries and arterioles in some cases these preceded the appearance of mild sclerosis

The rapidity of evolution of the renal changes in lupus nephritis varied greatly from case to case In our opinion the presence of severe fibrinoid changes local necrosis hematoxylin bodies and hyaline thrombi must be considered as evidence of marked activity of the lupus nephritis they were observed more commonly and were more severe during acute clinical exacerbations of SLE

3 THE RELATIONSHIP OF STRUCTURAL CHANGES IN THE KIDNEY TO RENAL FUNCTION

Addis introduced quantitative examination of the urinary sediment as an indirect means of observing the nature and extent of lesions affecting the kidney

TABLE XII

Results of urinalyses made just prior to histologic study (62 studies made)

Urine	Kidney							
	Normal	Glomerulitis		Glomerulonephritis				Total
		Membranous	Membranous and proliferative	Membranous	Membranous and proliferative	Subacute	Chronic	
Normal	12	4	3	0	0	0	0	19
Slight excess RBC only (3-12/HPF)	1	1	0	0	0	0	0	2
Slight excess WBC only (5-15/HPF)	1	0	0	0	2	0	0	3
Slight excess RBC and WBC	1	1	2	0	0	0	0	4
Excess WBC (5-15/HPF) Moderate number of casts	2*	0	2	2	3	0	0	9
Excess RBC and moderate number of casts	0	0	2	1	1	1	0	5
Large number of casts with or without excess RBC and WBC	0	0	0	5	2	6	7	20
Totals	17	6	[illegible]	8	8	7	7	62†

* One patient (#3) had had attacks of pyelitis. The other (#10) had nephrosclerosis.
† Includes studies made just before death.

(1) However, he recognized the diagnostic limitations of this method of study. (2) The technique of serial renal biopsies has offered us a unique opportunity to study directly the nature and extent of lesions affecting the kidney, and to compare and relate the pathology to the findings on urinalysis and to renal function assessed at the time of biopsy. These interrelationships will be discussed primarily from the point of view of the status of the urine and of renal function.

1. *Microscopic urinalysis*

(1) Normal urinalysis—

From Table XII it will be noted that the microscopic analysis of the urinary sediment was normal 19 times. In twelve instances the kidneys were histologically normal and in seven there was mild lupus nephritis (glomerulitis). In two patients (#6, 11) urinalysis and the renal histology were normal at the time of the first study; subsequently both developed membranous glomerulonephritis and leucocytes and moderate numbers of casts were found in their urine. Four patients (#12, 18, 19, 21) had glomerulitis when first studied, but no abnormality was found on microscopic urinalysis. When studied later three of these patients had developed glomerulonephritis, and the urinalysis had become abnormal in all four.

(2) Abnormal urinalysis—

On 43 occasions the urinalysis was abnormal (Table XII). In nine exam

nations there was a slight excess of leucocytes of erythrocytes or of both in the urine but not more than occasional hyaline or granular casts were found The kidneys of three of these patients were normal but when one (#11) subsequently developed a local and generalized membranous glomerulonephritis the urinalysis had become abnormal One patient in this group (#13) had four biopsies there was only a slight change in the renal lesion which progressed from glomerulitis to mild glomerulonephritis but leucocytes and erythrocytes were the only abnormality found on microscopic examination of the urine

On 14 occasions a moderate number of casts was found on examination of the urine All these urines contained 5–15 leucocytes, and five had 3–12 erythrocytes per high power field One of these patients (#3) had had acute pyelitis and another (#10) had benign nephrosclerosis neither had lupus nephritis In two (#12 14) membranous and proliferative glomerulitis was found on each of two examinations In one examination (#26) subacute glomerulonephritis was found membranous or proliferative and membranous glomerulonephritis was diagnosed in the other seven biopsies

On twenty occasions in eleven patients large numbers of casts were found in the urinary sediment All these patients had lupus glomerulonephritis membranous in five membranous and proliferative in two subacute in six and chronic glomerulonephritis in seven Nine of the eleven patients had nephrotic or pesudo nephrotic syndrome due to lupus nephritis All had excess numbers of erthyrocytes in the urinary sediment and on nine occasions there were 40 or more erythrocytes per high power field There were less than 5 leucocytes per high power field in six cases 5–15 in ten cases and more than 15 leucocytes per high power field in four cases Hyaline and granular casts were each found on nineteen occasions cellular casts (leucocyte or epithelial) on thirteen erythrocyte casts on four occasions and fatty casts or oval fat bodies on fourteen occasions Fatty casts and oval fat bodies were found on thirteen out of seventeen examinations in patients who had nephrotic and pseudonephrotic syndrome and in one patient (#33) who had chronic lupus glomerulonephritis

On 21 occasions an increased number of leucocytes was found in urines which contained no casts or a moderate number of casts In many of these urines the leucocytes were clumped and in a few, leucocyte casts were found This finding was reminiscent of the urine in pyelonephritis and in patients with clumps of leucocytes in the urine the diagnosis of lupus nephritis must be considered (78) Organisms were cultured from the urine of many of these patients but from one biopsy specimen only In only one patient (#3) was there clinical or histologic evidence of pyelitis or pyelonephritis Others developed evidence of infection later in the course of their disease when their kidneys were severely involved by lupus nephritis

As we are dealing with a single disease we can compare the relationship of abnormalities in the urinary sediment to the degree of histologic changes in the kidney From a study of Table XII it is clear that urinalysis is of value in assessing the extent of the renal involvement in lupus nephritis In the fifteen[7]

Two other patients had no evidence of lupus nephritis One (#3) had had attacks of pyelitis the other (#10) had nephrosclerosis These cases are excluded from this analysis

instances with normal kidneys microscopic examination of the urine was normal in twelve and in three there was only a slight increase of leucocytes, erythrocytes or both. Fifteen cases were diagnosed histologically as mild lupus nephritis (glomerulitis). Urinalysis was normal in seven; there were slight abnormalities but no casts in four, and there were a moderate number of casts in four cases. Thus in most cases with renal involvement confined to the glomeruli there were no casts in the urine, and in none of these cases was there a large number of casts.

In 30 instances biopsy sections were interpreted as consistent with lupus glomerulonephritis. In all but two instances casts were found in the urine, and were present in large numbers in twenty. The presence of many casts in the urine was a definite indication of glomerulonephritis—that is of structural damage to both glomeruli and tubules.

B Proteinuria

The amount of protein in the urine was measured either semiquantitatively (0 to 4+) on an early morning specimen of urine or quantitatively on a 24 hour urine specimen. Histologic observations on the presence or absence of proteinaceous material in Bowman's spaces and tubules were made in all cases, and these are summarized in Table XIII. In thirty-eight instances the patient had proteinuria at the time of the biopsy. Proteinaceous material was observed in the tubules of eleven, in Bowman's spaces only in one case, and in Bowman's spaces and tubules of the remaining twenty-six. In nineteen instances the patient did *not* have proteinuria when the biopsy was done. Proteinaceous material was found in Bowman's spaces and tubules in ten, and in the tubules only in six. Protein was not found in either Bowman's spaces or tubules in only three patients. The presence of proteinaceous material in Bowman's spaces and tubules of patients who have no measurable proteinuria constitutes additional evidence for the view that protein is normally filtered by the glomerulus and reabsorbed by the tubules (2, 135).

Proteinuria is a common finding in those conditions in which the glomerular basement membrane is thickened. For this reason an analysis was made not only of the total glomerular damage, but also of the changes in cellularity of the glomerulus and in the thickness of its basement membrane. The relationship between, on the one hand, proteinuria expressed quantitatively or semiquantitatively and on the other hand kidney damage, glomerular damage, hyper-

TABLE XIII

Relation of proteinuria to the presence of proteinaceous material in Bowman's space and in renal tubular lumina in 57 biopsy specimens

Proteinuria	Protein in Both Bowman's Space and Tubular Lumina	Protein in Bowman's Space Only	Protein in Tubular Lumina Only	No Protein Seen In Bowman's Space Or Tubular Lumina	Total
Present	26	1	11	0	38
Absent	10	0	6	3	19

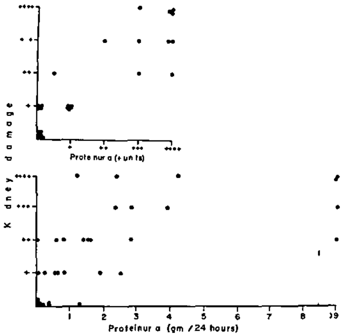


Fig 27 (a)

Fig 27 The relationship between the degree of proteinuria and the degree of (a) total kidney damage (b) glomerular basement membrane thickening (c) hypercellularity of the glomerulus and (d) tubular damage in patients ill with SLE who were studied by renal biopsy The amount of protein in the urine is expressed either in plus units or in grams per 24 hours Note that there is good correlation between the amount of protein in the urine and total kidney damage thickening of the glomerular basement membrane and tubular damage There is poor correlation between the amount of protein in the urine and glomerular hypercellularity

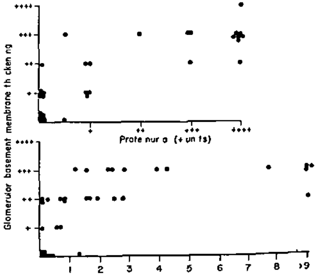


Fig 27 (b)

cellularity of the glomerulus, thickening of its basement membrane, and tubular changes, is shown in Figure 27 Study of the charts indicates that there was no correlation between hypercellularity of the glomerulus and proteinuria There was good correlation between the total kidney damage, glomerular damage or tubular damage and the amount of protein in the urine And there was obvious

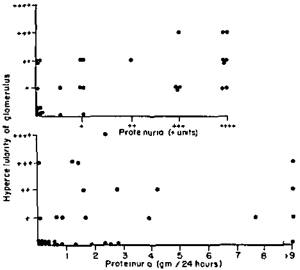


Fig 27 (c)

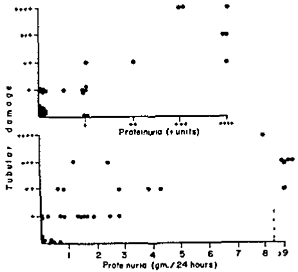


Fig 27 (d)

correlation between the changes in the glomerular basement membrane and the quantity of protein in the urine

C Tests of renal function

In their study of hypertensive patients before and after sympathectomy Talbott and his colleagues first demonstrated the value of studying the relationship between renal function and renal structure in the living patient Their studies were made using renal tissue removed at operation (281) The advent of a technique for percutaneous biopsy of the kidney has immeasurably widened the scope of such studies

Our patients have been studied over periods of time up to two years Studies of renal function were made just before each biopsy was taken and, in those who died within a few weeks of death Frequently studies were also made at varying intervals between biopsies During the two years of the study serial changes in the clinical and laboratory data were observed and compared with the histology on five and four occasions in cases #23 and 13 respectively, on three occasions in cases #6 7, 11 12 22 29 and 31, and on two occasions in twelve other cases Examples of these changes as observed serially are given in Figures 7 and 10

The methods used for the renal function studies and for the semi quantitative assessment of histologic changes are described in Section V For each biopsy the appropriate function was compared with the degree of overall kidney damage with the degree of glomerular damage, and with that of tubular damage Degrees of structural change were plotted on the ordinates of the graphs the function test on the abscissae

(1) Biochemistry of the blood—

The blood creatinine level was measured on 58 occasions at the time of the renal biopsy (Fig 28) It was 1 4 mg/100 ml or less in all sixteen cases with normal kidneys in sixteen of the seventeen cases in which kidney damage was estimated as 1+ and in seven of the ten cases in which the damage was 2+ In

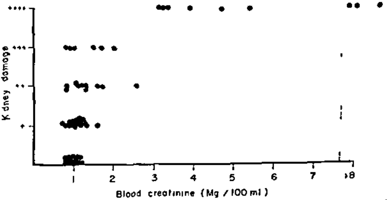


FIG 28 The relationship between the blood creatinine levels and the degree of kidney damage in patients all with SLE who were studied by renal biopsy (see text)

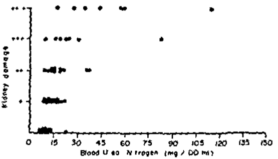


FIG. 29. The relationship between the blood urea nitrogen levels and the degree of kidney damage in patients ill with SLE who were studied by renal biopsy (see text).

two the level was 1.6 and 1.7 mg/100 ml, and in the third (#23, biopsy #1) the creatinine level was 2.6 mg/100 ml despite the fact that the histologic change was not gross. She was ill with the nephrotic syndrome and there was considerable edema of the interstitial tissue of the kidney. Moderate elevation of the blood creatinine levels has been observed in other patients with nephrotic syndrome—whatever the underlying pathology. In these patients, when the edema of the interstitial tissue has decreased after diuresis the creatinine levels have fallen towards normal. The creatinine level was less than 1.4 mg/100 ml in three of six cases in which there was 3+ renal damage, and between 1.4 and 2.0 mg/100 ml in the remaining three. It was greater than 3.0 mg/100 ml in all nine cases with 4+ renal damage. Thus the blood creatinine level remained within normal limits until the kidneys were severely damaged, and a raised creatinine level reflected only severe degrees of kidney damage.

The blood urea nitrogen was measured on 58 occasions (Fig. 29). The level of the BUN was 14 mg/100 ml or less in fifteen of the sixteen cases with normal kidneys, in ten of seventeen cases in whom the renal damage was estimated at 1+, in four of eleven cases with 2+ renal structural damage, and in one case with 3+ damage. The level was between 15 and 30 mg/100 ml in one case with normal kidneys, in seven with 1+ structural change, in five with 2+ damage, and in five with more severe changes. BUN levels of more than 30 mg/100 ml were encountered twice in patients with 2+ damage and in seven cases where the lesion was more advanced.

The blood non protein nitrogen was measured on 63 occasions (Fig. 30). The level of the NPN was 35 mg/100 ml or less in fifteen of the sixteen cases with normal kidneys, in only eight of the fourteen cases in whom the renal damage was estimated at 1+, and in seven of fifteen cases in whom it was 2+. In twelve cases with 1+ or 2+ renal damage the NPN level was in the range 35–50 mg/100 ml, and in two it was 60 mg/100 ml. In only two of the eighteen instances in which the renal pathology was 3+ or 4+ was the NPN less than 35 mg/100 ml.

Thus when the kidneys were histologically normal the level of serum creatinine was within normal limits in all cases, and the levels of BUN and NPN in all

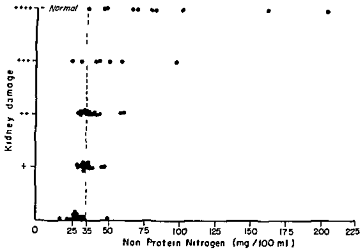


FIG 30 The relationship between the blood non protein nitrogen levels and the degree of kidney damage in patients ill with SLE who were studied by renal biopsy (see text)

but one instance With slight to moderate structural damage (1+ to 2+) the levels of BUN and NPN were raised slightly above the normal of 14 mg/100 ml and 35 mg/100 ml respectively in 43% and 41% of cases, and were considerably above normal values in 7% of cases By contrast the level of creatinine was raised slightly above the normal of 1 4 mg/100 ml in only 11% of cases with slight to moderate structural damage, and was considerably elevated in 4% Thus with slight to moderate structural damage the BUN and NPN were perhaps more sensitive indicators of the change in renal function than was the creatinine, on the other hand both BUN and NPN are subject to greater variation as a result of extrarenal factors such as dehydration and variations in the protein intake When the renal damage was more advanced (3+ to 4+) little difference was observed in the proportion of cases with elevated blood creatinine, BUN or NPN levels

As was expected the levels of urea nitrogen, non-protein nitrogen, and of creatinine in the blood did not reflect accurately the degree of underlying renal structural damage glomerular, tubular or both They were raised only when the damage was severe, and were not sensitive indices of loss of renal function

(2) Specific tests of renal function—

Specific gravity concentration tests were done within a few days of the renal biopsy on 43 occasions The results are shown in Figure 31 In general as the renal damage became more severe, the concentrating power of the kidney decreased, and this was found to be equally true when relationships with glomerular damage or tubular damage were assessed independently The figure 1 022 was taken as the lower limit of the concentrating power of the normal kidney The concentrating power was 1 022 or greater in nine of twelve cases with normal kidneys, in twelve of fourteen cases with 1+ kidney damage, and in four of seven cases with 2+ damage It was 1 020 in three cases with normal kidneys and in two with 1+ damage, and 1 018 to 1 020 in three with 2+ damage

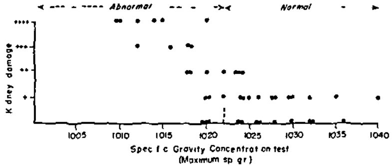


Fig 31 The relationship between the maximum urinary specific gravity and the degree of kidney damage in patients all with SLE who were studied by renal biopsy (see text)

In all ten cases in whom there was 3+ to 4+ damage the maximum specific gravity of the urine was less than 1 020 and it was 1 015 or less in five of the six cases with 4+ damage

Urea clearances were made in 51 instances (Fig 32) and the results were expressed as a percentage of average normal renal function (ANRF) The normal clearance was assumed to be 70% or more From Figure 32 it is seen that there was a close correlation between the urea clearance and the degree of renal damage Values of 70% or greater were found in eighteen instances with normal kidneys or 1+ damage in two with 2+ damage and in none where the damage was more severe Values of 50% to 70% ANRF were found in two instances with normal kidneys in eight with 1+ damage in three with 2+ damage and in one with a more advanced lesion Values less than 50% were not found until there was 2+ damage (five occasions) and were observed in twelve of the thirteen cases with more advanced lesions Thus the urea clearance test gave a fairly accurate estimate of the degree of overall damage to the kidney assessed histologically Similar results were obtained when glomerular damage and tubular damage were assessed independently

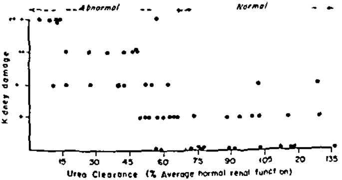


Fig 32 The relationship between the urea clearance (expressed as a percentage of average normal renal function) and the degree of kidney damage in patients all with SLE who were studied by renal biopsy (see text)

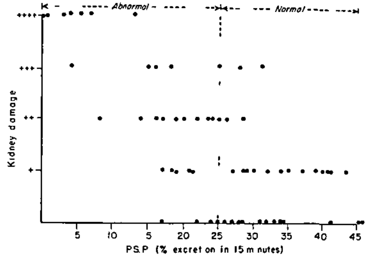


FIG 33 The relationship between the amount of phenolsulphonphthalein excreted in fifteen minutes and the degree of kidney damage in patients ill with SLE who were studied by renal biopsy (see text)

The excretion of phenolsulphonphthalein was measured fifteen minutes after intravenous injection The results of 59 studies are set out in Figure 33 Twenty-five per cent or more was excreted in 26 of 34 cases with normal kidneys or 1+ damage, in three of eleven with 2+ damage, in three of seven where the damage was 3+, and in none where it was 4+ It was between 15% and 25% *in fourteen of the remaining seventeen in whom renal damage was 1+ to 3+* In all seven cases with 4+ damage the excretion of PSP was less than 15% in 15 minutes and in six was below 8% Thus the 15 minute excretion of PSP gave an accurate estimate of the degree of renal damage

Conclusion In Table XIV the renal damage, estimated histologically, has been compared with the results of the specific gravity concentration, urea

TABLE XIV

The relationship between the degree of histologic damage and the number of abnormalities found when patients with SLE were studied by means of three simple tests of renal function

Renal Damage	Number of Cases*	All Three Tests Normal	One of Three Tests Abnormal: Urea clear	Sp gr conc	PSP	Total	Two of Three Tests Abnormal: Urea clear PSP	Sp gr conc PSP	Total	All Three Tests Abnormal
0	14	8	2	2	1	5	1	0	1	0
+	13	5	3	1	2	6	1	0	1	1
++	9	0	2	0	2	4	1	1	2	3
+++	6	0	0	0	0	0	1	2	3	3
++++	6	0	0	0	0	0	0	0	0	6

* Only cases in which all three tests were made are included in this table

clearance, and phenosulphonphthalein excretion tests It can be seen that when the kidneys were normal histologically, all three tests of renal function were normal in eight of the fourteen examinations that one test only was abnormal on five occasions and that both the urea clearance and PSP excretion were low on one occasion It should be emphasized that although tests of function were abnormal in six instances the degree of diminution in function was slight In cases with minimal histologic changes in the kidney (1+) all three tests of *function were normal in five of the thirteen examinations and all three were* abnormal in only one Again the degree of diminution of function was slight in respect of each test

With a moderate degree of kidney damage (2+) there was no instance in which all three tests were normal One was abnormal on four occasions two were abnormal on two occasions and all three were abnormal three times Of the six instances in which the kidney damage was estimated as 3+ two tests were abnormal on three occasions and three tests were abnormal on the other three With the most severe damage (4+) all three tests were abnormal on all six occasions

It has been shown above that the specific gravity concentration urea clearance, and PSP tests each reflected the underlying degree of kidney damage Nevertheless for each test there is a considerable biologic and experimental variation From Table XIV it is observed that any one of these three tests may be abnormal when the kidneys were histologically normal but that the degree of abnormality was slight In assessing the degree of kidney damage it is also seen that no single test was superior to the other two But a combination of all three tests gave an excellent overall impression of the underlying damage—a better assessment, in fact than when any one of the tests was used alone When the functional impairment was estimated by an assessment of all three simple tests taken together an accurate impression of the degree of histologic damage was obtained

VII THE CLINICOPATHOLOGIC FEATURES OF LUPUS NEPHRITIS

1 THE INCIDENCE OF LUPUS NEPHRITIS IN PATIENTS WITH CLINICALLY DIAGNOSED SLE

The criteria used by different investigators for the assessment of renal involvement in SLE are so variable that it is difficult to compare one study with another Many reports are based on abnormal urinary findings and interpretation of their data must depend on whether the proteinuria and cylindruria were permanent or whether they appeared transitorily during exacerbations of SLE. This consideration applies to the series reported by Jessar Lamont-Havers and Ragan (127) These authors found abnormal urinary sediments in 64% of their series of 44 cases and in 56% of the 279 cases reviewed by them Montgomery more accurately diagnosed renal involvement by the presence of *per-sister*

phrit

The

1938 and 1947 (191) Using these criteria 64% of the second series had evidence of renal involvement but only 13% of the first series It is difficult to account for this discrepancy It will be noted that the second series antedates the use of cortisone and corticotrophin therapy Thus increased longevity as a result of successful steroid therapy cannot explain the increased incidence of lupus nephritis from 1938 to 1947 These patients may have lived longer because of treatment with transfusions blood plasma, sulfonamides and penicillin In Harvey s series only 26 per cent of 138 patients had no signs of renal involvement Thus there was some evidence of affection of the kidney in 74% of his patients

The 33 patients reported here have not been followed for as long a time as those observed by Montgomery (190 191), Jessar (127) or Harvey (110) *Despite this 24 of 33 patients had renal involvement on histologic evidence* (i e 73%) Using the criteria of Montgomery, 21 patients have had *persistent proteinuria or cylinduria* due to lupus nephritis (i e 64%) in one additional case (#10) persistent proteinuria and cylinduria were the result of benign nephrosclerosis

As our clinical interests have covered the field of diseases of the kidney as well as that of SLE we considered it possible that our selection of cases may have been biased in favor of cases of SLE with renal involvement However it will be observed that the incidence of renal involvement in our patients was similar to that in other large series in which this bias did not exist Harvey and his colleagues (110) have also observed that structural damage to the kidney by SLE is more common than urinary findings and tests of renal function would have led them to believe

The assessment of renal involvement from post mortem material has been subject to considerable error for there are few studies in which the particular orientation of the authors has not played a part in the selection of their material Ten of our patients died and post mortem examinations were made on the kidneys of nine All had a glomerulonephritis These results are comparable with others For example Mook and his colleagues (193) examined the kidneys of 9 patients who died with SLE and found evidence of kidney involvement in all Baehr (9) found glomerular lesions in 78% of 23 post mortem examinations and Harvey (110) found some degree of involvement of the kidneys by SLE in 89% of 38 cases

We may therefore conclude that the kidney is involved by SLE in a high proportion of patients on clinical grounds about two thirds to three quarters of patients with SLE have lupus nephritis and on pathologic grounds an even higher proportion show evidence of kidney involvement

2 THE TIME OF ONSET OF LUPUS NEPHRITIS

The time of appearance of the first significant symptom has been taken as the time of onset of the disease In some cases a single sign or symptom (e g Raynaud s phenomenon polyarthralgia *biologic false positive test for syphilis*) occupied the stage for a long period of time and the duration of the disease

was interpreted in this light. In four patients (#24, 27, 30, 32) edema was the presenting symptom and made its appearance at the time of or shortly after the onset of other symptoms of SLE. Seven other patients (#22, 23, 25, 28, 29, 31, 33) presented to us with renal symptoms. However, all of these patients had had other symptoms or signs of SLE for from two to ten or more years. When first seen, all of these eleven patients had severe lupus nephritis (glomerulonephritis).

By contrast, in eleven patients renal involvement was initially discovered by urinalysis, by tests of renal function or by renal biopsy (#12–21 and #26). All had come to hospital primarily because of non renal manifestations of SLE. Only one of these patients had severe lupus nephritis when first studied (#26), and she died a few months later. Symptoms of SLE had been manifest for periods of from three months to eleven years in this group of patients. Eleven patients (#1–11) had no evidence of renal affection by SLE after periods of time which covered from 11 months to 9½ years. Two of these patients (#6, 11) subsequently developed lupus nephritis 17 months after the onset of their disease. We agree, therefore, with Hamburger and his colleagues (107) that the time of appearance of renal affection by SLE is variable: the kidney may become involved at the onset of the disease or at any time thereafter until just before death.

3. THE CLINICAL FEATURES OF LUPUS NEPHRITIS

Mild lupus nephritis. Ten patients had mild lupus nephritis when first seen. The glomeruli were affected but there was no significant involvement of the tubules. In none of these patients were renal manifestations a prominent feature of the clinical picture. In three no abnormalities were found in the urine, two excreted excess amounts of protein but no cells or formed elements, two had a slight excess number of erythrocytes, two excreted excess protein, red and white cells, and in only one patient were there casts in the urine in addition to protein and cells. There was a very slight increase of the blood NPN in two and a slight decrease in renal function in one. Three had persistently elevated blood pressures. In two hypertension appeared only during exacerbations of SLE. Thus in the early stages of renal involvement there was little to be found on clinical and laboratory examination.

Eight of these 10 patients with mild lupus nephritis have been studied serially by renal biopsy and four have developed evidence—both clinical and pathologic—of progression of their renal lesion. None has yet died. In none of these eight patients has there been any definite relationship between the frequency and severity of the exacerbations of SLE and the progression of their renal lesions.

Severe lupus nephritis. Twelve patients had severe lupus nephritis when first seen and their kidney lesions were classified as glomerulonephritis. By contrast with the ten patients with mild lupus nephritis, renal manifestations were a prominent feature of the clinical picture and in some cases they were the dominant feature. Nine of the patients had nephrotic edema.

In all twelve patients definite abnormalities were found when the urine was first examined Proteinuria was found in all, eleven had erythrocytes in the urinary sediment and these were present in large numbers in four, leucocytes were seen in the sediment of all but two and large numbers of casts were also observed in the urine of all patients Nine had azotemia and in two the NPN was at the upper limit of normal Renal function was decreased in nine and at the lower limit of normal in three Eight of these patients have died, seven of them in uremia The disease is progressing rapidly in two and more slowly in the other two Five patients in this group had hypertension, but in two it developed only within three months of death

Chronic lupus glomerulonephritis This has been an uncommon pathologic finding The lesions in three (#23 29 31)—diagnosed histologically as subacute glomerulonephritis when first seen—progressed to chronic glomerulonephritis and contraction of the kidney In addition to these three patient #33 had chronic glomerulonephritis when first studied The clinical course of these four patients progressed more slowly than that of those who died in the subacute stage of glomerulonephritis

The blood pressure was permanently elevated above 150/90 mm Hg in seven patients One (#10) a woman of 62 had nephrosclerosis but no evidence of lupus nephritis Case #16 ill with glomerulitis was the only patient with mild lupus nephritis who had an elevated blood pressure This may have been due to coincident essential hypertension Another (#29) has had a blood pressure of 160 90 mm Hg for about two years In the other four patients the blood pressure was raised for from two to twelve months before death in renal failure Excluding the patient with nephrosclerosis the blood pressure was elevated in six (i e 18%) This incidence is slightly higher than that reported by others (110 127) Hypertension was associated with advanced renal disease in four of the six patients and with moderately advanced renal disease in one On the other hand the blood pressure was normal in four patients who died in uremia These observations are similar to those of Harvey *et al* (110)

4 NEPHROTIC AND PSEUDO NEPHROTIC SYNDROME

By the nephrotic syndrome we mean that clinical state—regardless of its cause—which is characterized by edema massive proteinuria hypoalbuminemia and hypercholesterolemia The urinary sediment contains granular and hyaline casts and if they are carefully sought fatty casts and doubly refractile bodies are almost invariably found Allen (4) whose definition of nephrotic syndrome is essentially similar to ours states It is well known that in a high percentage of cases of disseminated lupus erythematosus with clinically significant renal involvement (approximately 33%) nephrotic syndrome develops Many authors have indeed mentioned the occurrence of nephrosis in SLE but the blood cholesterol values are often lacking in their reports and few have published all the essential data on their patients We have been able to find but seven reports of cases of SLE in which all the above clinical criteria of the nephrotic syndrome are fulfilled The first is the case of Brenner Leff and

Hochstein (35) reported in 1948 Two years later four cases were reported by Daugherty and Baggenstoss (63), another by Hamburger and his colleagues (107), and in 1953 Dubois reported a seventh (case #7) (66) In reports of *several large series of patients we have been unable to find cases of the nephrotic* syndrome with SLE Jessar, Lamont Havers, and Ragan (127) reviewed 279 published cases of SLE and added 44 of their own Although a number of these patients had proteinuria, hypoalbuminemia and edema there is no mention whether or not these findings were present in combination nor is there any reference to the levels of serum cholesterol In an extensive review of the literature on SLE Ross and Wells (248) do not mention the nephrotic syndrome and Kushniruk (160) likewise did not observe it in his series of 75 cases of lupus erythematosus Of the 138 cases of SLE recently reported by Harvey and his colleagues (110) only one (case #39) may have had the nephrotic syndrome and in this patient the cholesterol level was not recorded

Much to our surprise seven of the 33 patients in our clinical study manifested all the criteria of the nephrotic syndrome at some time during the period of study We have used serial renal biopsy as a tool in the study of the nephrotic syndrome (134 203) as well as in the study of the kidney affection in SLE This very fact may explain the large proportion of cases with nephrotic syndrome in our series An alternative explanation is more likely Most reports of large series of cases of SLE with nephritis have been made by *retrospective* studies of post mortem material and hospital records which may have been incomplete When we analyzed the available data on patients with SLE who died in our hospitals prior to 1952 we found that for our purposes adequate clinical and biochemical observations had not been recorded during the course of the patient s illness There were several such cases which might have been diagnosed SLE with the nephrotic syndrome but in only one of them (*G B*) were the data adequate to diagnose nephrotic syndrome in retrospect

In three of 33 patients in our clinical study all the criteria of the nephrotic syndrome were fulfilled *save that the serum cholesterol level was low* or within the normal range (Table VI) These three patients were all acutely ill and in all three the clinical course was one of rapid progress to death all three died within five months of the onset of edema Because these patients were similar clinically we coined the term pseudo nephrotic (202) to describe the syndrome Since these observations were made we have found a fourth case in our post mortem series (*M O*) who also had the pseudo nephrotic syndrome she died within one month of the onset of edema

Shearn and Pirofsky (259) called attention to a *clinical variant of the nephrotic syndrome* which occurred in patients ill with SLE Three of their four patients had cholesterol levels within the normal range and a fourth patient had an im

Sacks dise

had the fo

was 125 mg/100 ml, she died six months later

In 1940 Keil (139) had written Extreme hypercholesterolemia I have but

In all twelve patients definite abnormalities were found when the urine was first examined Proteinuria was found in all eleven had erythrocytes in the urinary sediment and these were present in large numbers in four leucocytes were seen in the sediment of all but two and large numbers of casts were also observed in the urine of all patients Nine had azotemia and in two the NPN was at the upper limit of normal Renal function was decreased in nine and at the lower limit of normal in three Eight of these patients have died seven of them in uremia The disease is progressing rapidly in two and more slowly in the other two Five patients in this group had hypertension but in two it developed only within three months of death

Chronic lupus glomerulonephritis This has been an uncommon pathologic finding The lesions in three (#23 29 31)—diagnosed histologically as subacute glomerulonephritis when first seen—progressed to chronic glomerulonephritis and contraction of the kidney In addition to these three patient #33 had chronic glomerulonephritis when first studied The clinical course of these four patients progressed more slowly than that of those who died in the subacute stage of glomerulonephritis

The blood pressure was permanently elevated above 150/90 mm Hg in seven patients One (#10) a woman of 62 had nephrosclerosis but no evidence of lupus nephritis Case #16 ill with glomerulitis was the only patient with mild lupus nephritis who had an elevated blood pressure This may have been due to coincident essential hypertension Another (#29) has had a blood pressure of 160 90 mm Hg for about two years In the other four patients the blood pressure was *raised for from two to twelve months before death in renal failure* Excluding the patient with nephrosclerosis the blood pressure was elevated in six (i e 18%) This incidence is slightly higher than that reported by others (110 127) Hypertension was associated with advanced renal disease in four of the six patients and with moderately advanced renal disease in one On the other hand the blood pressure was normal in four patients who died in uremia These observations are similar to those of Harvey *et al* (110)

4 NEPHROTIC AND PSEUDO NEPHROTIC SYNDROME

By the nephrotic syndrome we mean that clinical state—regardless of its cause—which is characterized by edema massive proteinuria hypoalbuminemia and hypercholesterolemia The urinary sediment contains granular and hyaline casts and if they are carefully sought fatty casts and doubly refractile bodies are almost invariably found Allen (4) whose definition of nephrotic syndrome is *essentially similar to ours states It is well known that in a high* percentage of cases of disseminated lupus erythematosus with clinically significant renal involvement (approximately 33%) nephrotic syndrome develops Many authors have indeed mentioned the occurrence of nephrosis in SLE but the blood cholesterol values are often lacking in their reports and few have published all the essential data on their patients We have been able to find but seven reports of cases of SLE in which all the above clinical criteria of the nephrotic syndrome are fulfilled The first is the case of Brenner Leff and

Hochstein (35) reported in 1948 Two years later four cases were reported by Daughertv and Baggensto s (63) another by Hamburger and his colleagues (107), and in 1953 Dubois reported a seventh (case #7) (66) In reports of several large series of patients we have been unable to find cases of the nephrotic syndrome with SLE Jessar, Lamont Havers and Ragan (127) reviewed 279 published cases of SLE and added 44 of their own Although a number of these patients had proteinuria, hypoalbuminemia and edema there is no mention whether or not these findings were present in combination nor is there any reference to the levels of serum cholesterol In an extensive review of the literature on SLE Ross and Wells (248) do not mention the nephrotic syndrome and Kushniruk (160) likewise did not observe it in his series of 75 cases of lupus erythematosus Of the 138 cases of SLE recently reported by Harvey and his colleagues (110) only one (case #39) may have had the nephrotic syndrome and in this patient the cholesterol level was not recorded

Much to our surpri e seven of the 33 patients in our clinical study manifested all the criteria of the nephrotic syndrome at some time during the period of study We have used serial renal biopsy as a tool in the study of the nephrotic syndrome (134 203) as well as in the study of the kidney affection in SLE This very fact may explain the large proportion of ca es with nephrotic syndrome in our series An alternative explanation is more likely Most reports of large series of ca es of SLE with nephritis have been made by *retrospective* studies of post mortem material and hospital records which may have been incomplete When we analyzed the available data on patients with SLE who died in our hospitals prior to 1952 we found that for our purposes adequate clinical and biochemical observations had not been recorded during the cour e of the patient s illness There were several uch cases which might have been diagno ed SLE with the nephrotic syndrome but in only one of them (*G B*) were the data adequate to diagnose nephrotic syndrome in retro pect

In three of 33 patients in our clinical study all the criteria of the nephrotic syndrome were fulfilled *save that the serum cholesterol level was low* or within the normal range (Table VI) These three patients were all acutely ill and in all three the clinical course was one of rapid progress to death all three died within five months of the onset of edema Becau e these patients were similar clinically we coined the term pseudo nephrotic (202) to describe the syndrome Since these ob ervations were made we have found a fourth case in our post mortem series (*M O*) who also had the pseudo nephrotic syndrome she died within one month of the onset of edema

Shearn and Pirofsky (259) called attention to a clinical variant of the nephrotic syndrome which occurred in patients ill with SLE Three of their four patients had cholesterol levels within the normal range and a fourth patient had an init

Sacks disc

had the fe

was 125 mg/100 ml she died six months later

In 1940 Keil (139) had written Extreme hypercholesterolemia I have but

rarely observed in cases of systemic lupus erythematosus In other instances the cholesterol value is normal or even diminished ' The explanation of these low serum cholesterol levels is quite obscure As in other patients with SLE the serum globulin level was raised and the thymol turbidity test was abnormal The cephalin flocculation and prothrombin times were normal The serum cholinesterase level was low (0 38 ΔpH units/hour) in the one patient in whom this observation was made This contrasts with the abnormally high levels of serum cholinesterase usually found in the nephrotic syndrome (295) In three cases the liver was examined post mortem and no histologic damage was observed It is nevertheless possible that SLE could produce some liver damage not detected histologically or by the limited tests of liver function performed in these patients Such undetected liver damage might depress hepatic synthesis of cholesterol but as Gould has pointed out the plasma cholesterol level falls only with severe liver insufficiency and cholesterol synthesis may be increased in the presence of slight liver damage (100) Squire has noted that the more severe degrees of hypercholesterolemia in the nephrotic syndrome were associated with extremely low levels of serum albumin (271) No significant difference was noted between the serum albumin levels in the two groups of patients with nephrotic or pseudo nephrotic syndrome

Careful analysis of the pathologic changes between the two groups revealed that the proliferative and basement membrane changes were of similar degree However hyaline thrombi wire loop lesions karyorrhexis hematoxylin' bodies and fibrinoid degeneration were observed more frequently and were more *severe in the pseudo nephrotic than in the nephrotic group of patients This* morphologic difference is surely the expression of a more acute and severe involvement of the glomeruli of the patients ill with the pseudo nephrotic syndrome

Cantarow and Trumper (44) *state that a low plasma cholesterol level* occurs in the terminal stages of a variety of diseases and that a fall from a previously elevated or normal level is of serious prognostic significance particularly if associated with increasing nitrogen retention It must be emphasized that in the pseudo nephrotic group the cholesterol levels were low *ab initio* This low cholesterol level with other features of the nephrotic syndrome in a patient ill with SLE has in our experience implied a grave prognosis and rapid demise

5 DISCUSSION OF PATHOLOGY

In the previous section the histologic features and evolution of lupus nephritis were set forth in detail It remains now to discuss the significance of the lesions their specificity and possible pathogenesis Lupus nephritis is a disease which affects predominantly the glomerular capillaries and their constituent elements In the earlier and milder stages of the disease the morphologic abnormalities are confined to the glomeruli, the tubules and interstitial tissue are involved later in the course of the disease However in a few cases which clinically are severe at the outset the tubules and interstitial tissue may be involved from the beginning

Clinically lupus nephritis does not run a protracted chronic course This may be due to one or more of the following reasons

1 The renal lesions progress more rapidly than those of most other renal diseases

2 Exacerbations are more closely spaced

3 Reversion to normal of glomerular lesions does not occur

4 In many instances the systemic nature of SLE contributes to the death of the patient before the renal lesions have evolved to a more chronic and less active form

Our studies indicate that the course and character of SLE and lupus nephritis may have changed during the past several years There is no doubt that the life span of these patients has been prolonged by treatment as a result renal changes tend to be more severe and chronic and less specific in character Certain changes have been produced in the kidneys of experimental animals by the administration of cortisone (30 240 241 287 301) and it is possible that treatment with cortisone could produce similar changes in man However the lesions seen in patients with lupus nephritis treated with cortisone are very different from those seen in the experimental animals and in the presumably normal kidneys of patients *with rheumatoid arthritis treated for long periods of time* with cortisone we have observed no abnormalities (230) Nevertheless it is conceivable that cortisone might modify the course and character of previously existing renal lesions and this treatment may have been a factor in lowering the incidence and decreasing the severity of certain changes such as wire loop lesions fibrinoid and hematoxylin bodies Unfortunately corticosteroid therapy does not prevent the progression of the renal disease

Our study again emphasizes the pleomorphic nature of the renal lesions in SLE (3 19 151) Because they are so pleomorphic it is misleading to classify lupus nephritis as a variety of membranous glomerulonephritis (3 4) An irregular local thickening of the glomerular basement membrane is the most consistent feature (19 151) and varying degrees of thickening were found in all specimens studied by us Nevertheless proliferative changes are common in the glomeruli and many other features are more typical of lupus nephritis than is thickening of the glomerular basement membrane

Many observers have stated that wire loop lesions are one of the most characteristic features of lupus nephritis but they have been noted in many other renal diseases (3 151 231 232) When they occur only in local areas at the periphery of the glomerulus and when they are associated with fibrinoid changes wire loop lesions are more strongly suggestive of lupus nephritis Moreover we wish to emphasize that wire loop lesions are not observed in the earliest stages and may disappear in the most advanced stages of the disease When wire loops are present they are not diagnostic of lupus nephritis unless associated *with other features more specific to this disease on the other hand* their absence does not exclude the diagnosis

As reported by others fibrinoid changes were frequently observed in lupus nephritis They were not universally present and in most instances especially

in the biopsy specimens, they were of mild to moderate severity. The relative scarcity of severe fibrinoid changes may be due to the fact that many biopsies were studied in an early or mild stage of the disease, and to the fact that most specimens were obtained during periods of relative clinical remission. Fibrinoid changes were more common and more severe when renal involvement was well established clinically, or when the biopsies had been taken from patients with acute exacerbations of SLE. The staining properties of fibrinoid suggested that it is closely related to but not identical with fibrin (7, 198, 296). With the methods used in this study we could not detect any differences between glomerular and arterial fibrinoid—differences which have been suggested by recent studies (32, 192). In a few instances fibrinoid was noted along an essentially normal glomerular basement membrane. This strongly suggests the possibility that circulating protein material is deposited from the blood onto the membrane. It is not clear whether this deposition is related to the quantitative and qualitative changes in the serum proteins which occur in SLE.

The occurrence of local and focal glomerular necrosis has been reported by several investigators (19, 151). Although Klemperer and his associates described this lesion in detail its importance and frequent occurrence were overlooked until Smith's recent study (264), its nature, however, is not well understood. Morphologically it is similar to the lesion of embolic glomerulonephritis described by Lohlein (172), and the possibility of an embolic etiology cannot be excluded entirely even in the absence of microorganisms in the blood and tissues. In none of the patients studied was a definite diagnosis of Libman Sacks endocarditis made, moreover it is unlikely that the firm, verrucous vegetations of Libman Sacks endocarditis could be responsible for embolic manifestations.[8] Therefore it is probable that the glomerular necrotic lesions are primarily the result of local ischemia from coalescence of capillaries, basement membrane thickening, fibrinoid changes and endothelial cell proliferation. This lesion, which is unusual in other renal diseases with glomerular ischemia, may be due to several factors including the rapidity of development of the capillary obstruction and the local release of abnormal substances peculiar to SLE (159).

Hematoxylin—or more accurately "hematoxyphil" (264)—bodies were found relatively infrequently in our material. This was probably a reflection of the high proportion of early lesions studied, and of the fact that only a limited number of glomeruli was available for study in each biopsy specimen. Nonetheless they were found in a few biopsy specimens in which the immediate fixation of the living tissue excludes the possibility that the formation of "hematoxylin" bodies results from agonal or postmortem changes. Their common occurrence in areas where pyknosis, karyorrhexis and karyolysis are seen points to their probable origin from nuclear material and to their close relationship to the Har-

[8] It is of interest that ev
in only one of the thirty c
of Gross (103) who found
tion of Jessar (127) and Harvey (110), each of whom observed this lesion in approximately one third of their patients. This difference in incidence is difficult to explain but the recent experience of other pathologists has been similar to ours (231, 252).

graves s cell phenomenon (25, 104 109 150 162) It is not clear why hematoxylin bodies should be specific for SLE Save for two cases (228 306) one of which might have had SLE, they have not been observed in any other renal disease including those associated with necrotizing lesions of the glomeruli

'Hyaline' thrombi in the glomerular capillaries are usually observed in the advanced and active stages of lupus nephritis but are not peculiar to lupus nephritis (128) They appear to consist primarily of fibrin and platelets The mild to moderate basophilic smudging which is observed in some instances may be due to the presence of material of nuclear origin and differentiation form intraluminal 'hematoxylin' bodies may be difficult in these cases 'Hyaline' thrombi must also be differentiated from eccentric fibrinoid thickening of the capillary wall—the so called vertucal capillaritis (3) Their pathogenesis is obscure, we agree with Jones (128) that alterations in the lining cells of the capillaries and slowing down of the circulation probably play a role in their formation

Clumping and proliferation of the endothelial cells of the glomerular tuft is common in lupus nephritis (19 272 274) as well as in many other renal diseases In lupus nephritis this cellular proliferation usually affects small areas rather than the whole of the glomerular tuft and the degree of endothelial cell proliferation is not comparable in severity to that seen in cases lying of acute glomerulonephritis Our findings suggest that endothelial cell proliferation follows the development of changes in the glomerular basement membrane By contrast proliferation of epithelial cells and the formation of fibroepithelial crescents is a late manifestation of lupus nephritis Thus in most cases of lupus nephritis proliferative changes are found in the glomeruli in addition to the membranous changes

The lack of specificity and the difficulties of interpretation of the tubular changes in lupus nephritis have been discussed in the previous section As in many renal diseases 'hyaline droplets' are observed in the cytoplasm of the convoluted tubular cells their reactivity with PAS is not as marked as in the kidney of amyloidosis and of multiple myelomatosis The accumulation of hyaline' droplets is the result either of excessive resorption by or of altered metabolism of the tubular cells (211) Unfortunately it was impossible to carry out satisfactory mitochondrial stains on our material better to evaluate this process

Edema of the interstitial tissue of the kidney is a frequent finding This correlates well with the swollen gross appearance of the kidney at autopsy, and with the frequent occurrence of nephrotic and pseudo nephrotic syndrome Interstitial fibrosis occurs even more commonly but is rarely sufficiently severe to cause gross contraction of the kidneys

With the exception of 'hematoxylin' bodies no other single histologic feature can be considered characteristic or pathognomonic of this disease Nevertheless the histologic diagnosis is relatively easy in many cases as some histologic features occur frequently in a combination peculiar to lupus nephritis (e g 'wire loops', focal necrosis fibrinoid and hematoxylin bodies) Accurate

histologic diagnosis is more difficult in the early stages before these lesions have developed However, the local involvement of small areas at the periphery of the glomerulus by *membranous or membranous and proliferative changes was found* to be of great value in diagnosis in the early stages Diagnosis is also more difficult in the late chronic stages when the typical lesions have become obscured by the chronicity of the process Except for non specific glomerulonephritis differential diagnosis does not present a serious problem The histologic differentiation from other diseases which may simulate SLE clinically is discussed in section (X) below

Although the systemic nature of the connective tissue changes in SLE is well known it is not clear whether involvement of the kidneys in SLE is a primary or a secondary manifestation of the disease The kidneys are not always involved early in the disease but are affected ultimately in a very high proportion of patients It is possible that *renal involvement in SLE is a secondary mani*festation such as a reaction to one or more abnormal circulating substances derived from either the connective tissue itself or from the reticuloendothelial system—both connective tissue changes and reticuloendothelial hyperplasia are known *to occur in SLE In our patients however the development of lupus* nephritis was not *specifically* preceded by or related to any one or combination of clinical or laboratory abnormalities Thus it seems more probable that lupus nephritis is a primary manifestation of the generalized involvement of the connective tissue

VIII TREATMENT OF LUPUS NEPHRITIS

1 GENERAL MEASURES

The treatment of SLE has been reviewed extensively in recent publications (55 67 110 267 269) and the therapeutic response of SLE to cortisone and corticotrophin is well known We will therefore limit this discussion to certain aspects of the treatment of lupus nephritis

The prevention and treatment of acute exacerbations of the disease are of prime importance Intercurrent infections especially of the upper respiratory tract dental extractions (141) drug reactions (95 97) exposure to sunlight and other stimuli have been reported to precipitate acute exacerbations of the disease One of our patients (#23) had an exacerbation of SLE a recurrence of nephrotic syndrome and an increase of hematuria following an upper respir*atory tract infection In another patient (#30)* who was severely ill further deterioration of SLE and of lupus nephritis occurred after dental extraction In two others (#21 31) the face rash became more prominent and the general symptoms and signs of SLE recurred after exposure to sunlight In one of these patients there was an increase *in the histologic damage to the kidney* but this may have been coincidental One patient (#18) who had many acute exacerbations and was not free from symptoms despite large doses of prednisone (30 60 mg daily) became acutely ill whenever she indulged in excessive physical exertion All these precipitating factors must be avoided as far as possible exacerbations should be anticipated after infections and during and after preg

TABLE XV

Relationship of previous treatment with ACTH or Cortisone to the degree of kidney pathology found at the time of the first histologic study

ACTH or Cortisone Therapy Before First Study	Kidney Pathology at the Time of First Study			Total Cases
	Normal	Glomerulitis	Glomerulonephritis	
Yes	8	7	7	22
No	3	3	5	11

TABLE XVI

Effect of treatment with ACTH and cortisone on the progression of renal lesions in 21 patients with SLE

Hormone Therapy between First and Last Histologic Study	Kidney Damage			
	Improved	Unchanged	Progressed +	Progressed ++
Yes	0	4	11	2
No	0	2	1	1

nancy They must be treated vigorously and with a sense of urgency if and when they arise Once clinical and histologic evidence of lupus nephritis had appeared, treatment was symptomatic

A *The prevention of lupus nephritis*

When the 33 patients in this series were first studied by us 22 or 67% had histologic evidence of renal involvement compatible with SLE, and two others (#6 11) subsequently developed renal lesions of SLE At present corticotrophin and [illegible]
resu
SLE
suppress the clinical manifestations no effect of the steroids was demonstrable in preventing the development of lesions We must conclude that there is at present no way in which the development of lupus nephritis can be prevented in the patient with SLE

B *Nephrotic and pseudo nephrotic syndrome in lupus nephritis*

These patients were kept in bed for varying lengths of time and in one, diuresis ensued spontaneously (#23) High protein feeding (up to 1 5 kg/kilo/day) and dietary sodium restriction were aimed at in all cases, but in almost all of these patients there was fairly severe renal damage, and permanent azotemia necessitated a limitation of the protein intake The patients with pseudo nephrotic syndrome (#28 30 32) were all extremely ill and required very strict bed rest and meticulous nursing care One of them (#28) received 500 mg hydrocortisone each day intravenously the second (#30) was treated

with 75 to 100 mg cortisone daily, and the third (#32) received no steroid In no case was there any detectable effect of treatment on the outcome

C Chronic renal failure in lupus nephritis

In general the aim of treatment was to allow the patient to lead as normal a life as possible In all cases the dietary protein intake was limited usually to about 40 gm daily The patients were carefully instructed about the importance of an adequate fluid intake and urinary output The fluid intake (2500 3000 ml 24 hours) was spread through the 24 hours and we insisted that they drank 2 to 3 glasses of water at night before retiring These two measures in combination were perhaps the most important factors in preventing rapidly advancing azotemia in those with chronic renal failure

In patients who were treated with corticotrophin or cortisone the sodium intake was kept below 2 gm (85 meq) daily, but sodium restriction has not proved necessary in patients receiving prednisone Patients with the nephrotic or pseudonephrotic syndromes and some of those with chronic renal failure were limited to 500 mg (22 meq) of sodium daily Patients with chronic renal failure were closely observed in the outpatient department Frequent electrolyte determinations enabled us to anticipate and treat serious electrolyte imbalance in some cases This was usually done by limiting the electrolyte intake in the diet as the need arose Phosphorus was on occasion limited to 600 800 mg/day and potassium to 1000 mg (25 meq) or less Sudden and fatal hyperpotassemia (#32) cannot always be prevented by dietary means especially when the patient is severely ill and there is widespread tissue breakdown Ion exchange resins 50% glucose intravenously with insulin and calcium were used to prevent sudden cardiac arrest due to hyperpotassemia Calcium lactate in doses of 9 gm daily and vitamin D 10 000 units daily were given to patients in whom the levels of serum calcium were low Supplementary sodium bicarbonate was sometimes necessary to combat hyperchloremic acidosis Nausea and vomiting were well controlled by chlorpromazine Initially it was given in doses of 25 mg 6 hourly by intramuscular injection When the vomiting was controlled the intramuscular injections were stopped and the drug was given by mouth

Anemia may be due to the effects of SLE on the bone marrow or to a hemolytic process (#1) It usually responds well to treatment of the disease with cortisone or corticotrophin (67) On the other hand if anemia was associated with significant azotemia steroids were of no value and transfusions of packed red cells were given As reactions to blood transfusion are not uncommon in patients with SLE cross matching should be meticulous and Coombs's tests should be done routinely Transfusions should be given only as the general symptoms warrant for no improvement in renal function occurs in the patient whose hemoglobin is raised to normal (251) and Platt has suggested that glomerular plasma flow may be adversely affected by a substantial increase in the hematocrit (227)

Transient hypertension occurred during acute exacerbations of SLE (#5) and usually responded to treatment of the exacerbation with cortisone or corticotrophin Permanent hypertension occurred infrequently as patients usu

ally died before the stage of chronic glomerulonephritis Those with hypertension were treated with small doses of reserpine and/or pentolinium The history of case #31 (Fig 7) illustrates the successful management of a patient with SLE and chronic renal failure In October 1953 this 23 year old student was severely ill with grand mal seizures hypertension severe acidosis tetany and anasarca After recovery from this acute episode he was treated as outlined above and was able to continue working eight hours daily until three weeks before his death in August 1955 During the whole of this period he was admitted to hospital once at our request and once for blood transfusion

2 THE EFFECTS OF CORTICOTROPHIN AND CORTISONE ON LUPUS NEPHRITIS

In 1951 Rich and his co workers reported that the development of experimental anaphylactic nephritis in rabbits (242) was prevented by the administration of corticotrophin (ACTH) (23 241) When cortisone was given instead of ACTH anaphylactic nephritis did not develop however a different type of lesion appeared (240) Subsequently they showed that these lesions were produced by cortisone alone (241) The lesions were characterized by dilatation of the glomerular capillary loops focal necrosis of cells of the loops and the formation of large hyaline masses in the tufts There was frequent rupture of the tufts and considerable hemorrhage in the tubules The lesions were similar in appearance to the glomerular lesions in diabetes mellitus described by Kimmelstiel and Wilson (142) Bloodworth and Hamwi (30) and Wilens and Stumpf (301) have also produced similar lesions in rabbits with cortisone Harvey and his colleagues (110) stated that they had observed similar lesions in one patient with SLE, but no histologic description was given

Without doubt corticotrophin and cortisone are of great value and may be life saving in acute exacerbations of SLE (42 55 67 266 269) The early experiences of numerous investigators (41 42 45 71 118 266 268 288) led them to conclude that the renal lesions of SLE were seldom benefited by corticotrophin or cortisone Dubois (67) and Haserick (113) however noted a decrease in the hematuria and proteinuria in some patients given large doses of cortisone but in three patients with SLE treated with cortisone Janeway (125) noted a marked exacerbation of the renal picture as determined from the Addis count Particularly noticeable was the tremendous increase in albuminuria When these three patients were treated with ACTH there was very little alteration in the renal picture Soffer and Bader (266) observed that hematuria and cylinduria persisted despite treatment In five of their ten patients with azotemia the blood urea nitrogen returned to normal levels when the patients were rehydrated and their clinical condition had improved Harvey and his colleagues (110) made similar observations and at the post mortem examination of several patients treated with corticotrophin and cortisone for long periods of time they found no renal disease Recently Bollet Segal and Bunim (31) treated four patients with SLE and lupus nephritis with up to 30 mg of prednisone daily They found no improvement in the renal status and no significant change in the quantity of proteinuria

Dubois (66) reported that the early "mild nephropathy" cleared with treat-

ment. Two of his patients improved after treatment with cortisone but evidence of renal involvement appeared again during exacerbations a few months later. Soffer and his co-workers (269) did not observe an increased rate of progression of the renal lesions as a result of corticotrophin or cortisone therapy in 55 patients. They also emphasized that hormonal therapy had no effect on the hypertension associated with underlying renal disease. On the other hand, Harvey (110) observed elevation of the blood pressure and rapid accumulations of fluid in seven patients with SLE and lupus nephritis who were treated with corticotrophin and cortisone. In five the change was so rapid that hormonal therapy had to be stopped.

In a small number of patients with SLE treated with hormones, Soffer (269) observed a significant improvement in renal function. Heller, Jacobson and Hammarsten (118) studied the protein excretion, urinary sediment and tests of discrete renal functions in two patients with SLE and in four patients with glomerulonephritis. They concluded that cortisone had no beneficial effects upon the basic pathologic process in the glomerular capillaries.

Of the present series of 33 patients, 22 had received corticotrophin or cortisone before the first biopsy was made (Table XV). Seven had histologic evidence of severe kidney damage and in eight the kidneys were normal. Eleven patients had received no hormone therapy before the first biopsy. Five of this group had pathologic evidence of severe kidney damage and in three the kidneys were normal. In twenty-one patients serial histologic examinations were made (Table XVI). A decrease of kidney damage assessed histologically was not observed in any patient. Seventeen patients were treated with hormones between the time of the first and the last histologic study. The doses used were those which were sufficient to suppress symptoms and in no case did the maintenance dose exceed 200 mg of hydrocortisone daily or its equiv... [illegible] ...hirteen of the ... pa-tients the renal lesion progre...ed and in ... change

Four patients were not treat... t and ... was the last histologic study. In t... noted, whereas in the other ... logic material we did not fi... by cortisone in rabbits.

The numbers of patients ... tion of patients. Treatmen... Unfortunately we did not ... to the kidney following t... we can find no evidence t... of the renal lesion ... for ... was the same in those pa... who had never received ...

The literature on progn... out elsewhere (110, 184).

starting point of the disease Until recently SLE was considered to be an acute or subacute disease, and the less dramatic symptoms and signs which may have been present for years were overlooked With increasing interest in and experience of the disease it has now been recognized that past episodes such as Raynaud's phenomenon arthralgia thrombocytopenic purpura and hemolytic anemia were not independent disease entities but were due to activity of SLE (290) Moreover as pointed out by Moore and Lutz (196) and by Haserick and Long (114), biologic false positive serologic tests for syphilis may be observed for many years before the patient develops symptoms or signs of SLE Thus it is apparent that it may be difficult or impossible to date the onset of SLE which does not necessarily coincide with the appearance of the first florid attack of the disease

Evidence that SLE is frequently a chronic rather than an acute or subacute disease was presented in 1955 by Merrell and Shulman (184) In their series of 99 patients the time between the estimated onset and the date of diagnosis varied from less than one month to 35 years Analysis of their data reveals that this latent period was over ten years in twelve patients it was from five to ten years in seventeen patients from two to five years in twenty six patients and it was two years or less in forty four patients Baehr Klemperer and Schifrin (9) reported that the maximum survival time was 4½ years from the time of onset but this report is twenty years old and more recent reports contain numbers of cases in which the disease has been present for many years (22 110 111 127 290) As the course of the disease may be so prolonged and as the initial symptoms may be insidious and are extremely variable it is often difficult to define exactly the date of onset The duration of the disease from the appearance of the first symptoms to the time of our initial study is shown graphically in Figure 34 In most, but not all cases the time of our initial study corresponded closely with the time of diagnosis From Figure 34 it will be noted that in the majority of cases (57%) the duration was less than two years but that in four cases (12%) it was between five and ten years and in five cases (15%) it was between ten and fifteen years Because of the difficulty in assigning an exact

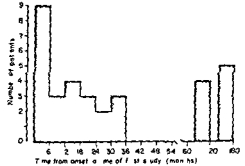


FIG 34 Histogram showing the length of time from the onset of the first symptom of SLE until the date of the first renal biopsy done in 33 patients ill with SLE

date of onset in these patients, it is likely that these figures are somewhat inaccurate. If so, they err in underestimating the duration of the disease.

Harvey and his colleagues (110, 196) studied two specific factors with respect to their effect on prognosis, namely, age at the time of diagnosis and the duration of time from onset to diagnosis. They found no significant difference between the survivorship curves of patients under and over 40 years of age, and in respect of the second point, they concluded that "the type of case that presents serious enough symptoms early in its course to bring the patient to the attention of the doctor and enable him to make a diagnosis *may well be the type that progresses more rapidly thereafter*." Our series is too small to analyze in respect of these two general points of age and duration of the disease, but much can be *gleaned from a close study of the course of a single manifestation* of the disease—namely, the renal involvement.

2. PROGNOSIS IN LUPUS NEPHRITIS

de

no

ever, protein and formed elements may appear in the urine of patients with SLE during acute exacerbations (110, 269), and these abnormalities may disappear either when spontaneous remission occurs (273) or as a result of therapy (42, *110, 269*). This has been our experience.

Keith (140) in 1940 did not believe that renal insufficiency played an important role in causing death, but the opposite view had been advanced by Snapper in 1935 (265). He drew attention to the importance of the renal lesion

picted below.

In Table XVII findings on 33 patients are presented. The patients will be discussed on the basis of the clinical and pathologic criteria previously described. When first studied, eleven had normal kidneys. Nine are still living; one (#8) *died of an acute exacerbation of SLE, and the other (#11)* of acute anterior poliomyelitis. She was not azotemic at the time of her death, but a membranous lupus glomerulonephritis was found at post mortem examination. None of the ten patients with mild lupus nephritis (glomerulitis) has died, but four (#14, 18, 19, 21) have developed clinical and pathologic evidence of progressive renal *involvement*.

Twelve patients had severe lupus nephritis (glomerulonephritis) when first studied. Eight have since died, and only one (#29) enjoys moderate health *despite a mild degree of azotemia*. Six of these patients had the nephrotic syndrome, and four have died in uremia. Of the others, two (#24, 29) have mild azotemia and impairment of renal function. Three patients had the pseudo*nephrotic syndrome (proteinuria, hypoalbuminemia, edema, and low* serum cholesterol). All died within weeks of the onset of edema. The gravity of the

TABLE XVII

Duration of illness and clinical study of 33 patients with SLE a clinicopathologic presentation

Mode of Presentation	Number of Patients	Duration of Illness Before First Study*	Duration of Study*	Number Living: Moderate health	Number Living: Ill health	Number Living: Prog renal invol v	Number Living: Total	Number Dead
I Normal kidneys	11	48 (3–180)	11.7 (3–23)	6	3	0	9	2
II Glomerulitis	10	26 (3–132)	12.2 (3–23)	5	5	4	10	0
III Glomerulonephritis	12	46 (3–180)	6.5 (0–24)	1	3	4	4	8
(IIIa) Nephrotic syndrome	7	30 (3–72)	12.0 (1–24)	1	2	2	3	4
(IIIb) Pseudo nephrotic syndrome	3	6 (5–6)	0.5	0	0	0	0	3

* Average in months for the group. Range given in parentheses.

prognosis in SLE with the nephrotic and pseudo nephrotic syndrome is thus clearly shown, and these results confirm the findings of Daugherty and Baggenstoss (63) and of Shearn and Pirofsky (259).

In essence thirty-three patients with SLE have been followed for periods of up to two years. Ten have died within this period giving an overall mortality rate of 30%. Of those who died six died of severe renal failure and one of acute pancreatitis due to fibrinoid necrosis of pancreatic vessels. This patient (#27) who had the nephrotic syndrome was severely uremic. Another died of an acute attack of SLE and myocarditis (#28). She had pseudo nephrotic syndrome azotemia and severely damaged kidneys. Patient #11 had developed renal damage but was not in renal failure when she died from intercurrent acute anterior poliomyelitis. Patient #8 died from an inadequately treated exacerbation of SLE (acute lupus crisis). She was the only patient in whom there was no evidence of lupus nephritis.

X THE RELATIONSHIP OF SLE AND LUPUS NEPHRITIS TO OTHER DISEASES

1 GLOMERULONEPHRITIS

Few modern texts of medicine mention SLE as a possible cause of renal disease simulating glomerulonephritis acute subacute or chronic. As SLE has become a more common—or more commonly recognized—clinical entity its relationship to glomerulonephritis has assumed an increased importance. In recent years many authors have pointed out that the presence of a skin rash is not a *sine qua non* for the diagnosis of SLE and skin rashes are not infrequently absent in patients with lupus nephritis. This was first reported by Brenner (35) and subsequently stressed by Hamburger (107). Recently Marmont (178) reported five cases of SLE without a skin rash, two had proteinuria and the other three died in renal failure.

If no skin rash is present, other symptoms and signs may be overlooked, if they are found their full importance may not be realized Milne (187) rightly stressed the necessity of a broad clinical perspective in arriving at the correct diagnosis The following case history illustrates this point

Case #32

B D (R & E 427597) an attractive 18 year old high school student had enjoyed good health until June 1954 After a period of exposure to the sun she developed erythematous spots on the forearms and face In July she had transient ankle edema which recurred one month later Gross proteinuria and hematuria appeared a diagnosis of Bright's disease was made and she was confined to bed On November 1st she was admitted to the University of Illinois Hospitals where periorbital and pretibial edema was noted Much blood and protein was found in the urine a few leucocytes and many hyaline granular fatty and erythrocyte casts were seen in the urinary sediment The serum albumin was 2 3 gm/100 ml the serum globulin was 3 3 gm/100 ml the blood cholesterol was 132 mg/100 ml and the NPN was 98 mg/100 ml She was able to concentrate her urine to a specific gravity of only 1 015 the urea clearance was 11% of ANRF, and the excretion of PSP was 3% in 15 minutes A diagnosis of subacute glomerulonephritis was made

However careful review of the history revealed the following additional information At the beginning of the illness she was feverish and had noted arthritis of the interphalangeal joints In October she had pain in the shoulder joints and complained of pleuritic pain On examination there was a persistent fever, a faint butterfly face rash was detected the liver was enlarged, there were effusions into pericardial pleural and peritoneal cavities the leucocyte count was $3500/mm^3$ and the thymol turbidity was 12 units This additional evidence made a diagnosis of SLE with lupus nephritis very probable and many Hargraves's cells were found on examination of the bone marrow She became comatose had several convulsions and died on November 15 Permission for a full postmortem examination was refused but kidney tissue was obtained postmortem with a biopsy needle

Postmortem Biopsy (Color Plate—Fig 9) The glomeruli were ischemic and there were local areas of irregular smudgy thickening of their basement membranes Local areas of hypercellularity were also seen The lumina of a few glomerular capillaries were filled by homogenous eosinophilic material these capillary thrombi were PAS positive and stained red in Mallory preparations (Color Plate—Fig 10) Distinct wire loops karyorrhexis and hematoxylin bodies were seen in a few glomeruli (Color Plate—Fig 9) A few adhesions between glomerular tufts and Bowman's capsule were noted Proteinaceous material was observed in Bowman's spaces and in the convoluted tubules whose lining epithelium showed considerable atrophy and degenerative changes There was edema and fibrosis of the interstitial tissue which was infiltrated by chronic inflammatory cells There were fibrinoid changes in the small arteries

Diagnosis Lupus nephritis subacute local and generalized membranous and proliferative glomerulonephritis

The pathologic differentiation of lupus nephritis from glomerulonephritis may be difficult (Section VI (2E) and Table XI) In the early stages of the condition the local involvement of small areas of the periphery of the glomerulus by membranous and proliferative changes (Color Plate—Fig 1) has been, in our experience, peculiar to lupus nephritis, whereas in glomerulonephritis the whole or almost all of the glomerulus is usually involved Nonetheless we have seen lesions in the early stages of glomerulonephritis, which have been difficult to distinguish from those of lupus nephritis For example, in Ellis's, Enticknap and Joiner's excellent clinical and pathologic study of Bright's disease (75) Figure 1 is taken

from the kidney of a patient diagnosed clinically as Ellis type I ne... A pathologic diagnosis of Ellis type II nephritis was made by th... local area of necrosis local hypercellularity and karyorrhexis ... ening of the glomerular basement membrane are prominent feature ... tunately the clinical history of this patient was not given but the pathol... features are more consistent with the diagnosis of lupus nephriti

In his Croonian lectures in 1942 Arthur Ellis wrote "Much of th... which still exists in our knowledge of the conditions grouped und... Bright's disease arose from failure to study the natural history ... ditions—their mode of incidence and subsequent course to ... (72) Case 31 (page 42) is an excellent illustration of the valu... in the study of the natural history of renal disease and ... tance in arriving at an exact pathologic diagnosis In Sept ... t ent developed symptoms and when seen by us for the first ... had the classical clinical and laboratory picture of SLE ... his urine A renal biopsy made in September 1953 was con... nosis of lupus nephritis (Color Plate—Fig 7) Fibrinoid ... the glomerular basement membrane and in the arteriole ... areas of karyorrhexis A second biopsy in April 1954 reve... (Color Plate—Fig 8) In these biopsies there were featur... chronic lupus glomerulonephritis respectively From th... t nts clinical and laboratory course came more and more to a case of chronic glomerulonephritis without SLE and at ... ton in August 1955 the renal lesion was quite indistingui... ... kidn... ... s of chro... gl... nephritis would undoubtedly have been made Yet taking into account the cli... cal laboratory and pathologic features studied serially over a period of years there was no doubt that this was a case of SLE with lupus neph...

2 POLYARTERITIS NODOSA

Polyarteritis nodosa may run a prolonged remittent course and like SLE affect many organs and systems of the body Consequently the differential diagnosis may be a difficult one as has been emphasized by Banks (14) Klemperer (131) Pagel (219) and others In 1928 Volk (293) reported a case of typical SLE in whom lesions characteristic of polyarteritis nodosa were found postmortem recently Lincoln and Ricker (169) and Kofman Johnson and Zimmerman (156) reported cases of histologically proven polyarteritis nodosa in whom Hargraves's cells were found

We have observed three patients in whom the problem of the relationship between polyarteritis nodosa and SLE arose Case #10 had features common to both diseases Hargraves's cells were found on examination of the peripheral blood and polyarteritis nodosa was found on examination of a muscle biopsy The following case is presented because her clinical course was typical of that

nodosa runs a prolonged course characterized by exacerbations and remissions It is a recurrent progressive inflammatory disease of the muscular type of arteries Fibrinoid necrosis was a prominent pathologic feature and involvement of the kidney almost universal (29 154 307) Renal infarcts were the prominent pathologic lesion but were not extensive enough to result in renal insufficiency A similar pathologic picture was described by Davson Ball and Platt in five of their cases (their Group B) (64)

The lesions described in hypersensitivity angiitis by the Cincinnati workers were very different (154) A necrotizing glomerulonephritis was found in nine of their ten cases Exudation and necrosis rather than proliferation of epithelium and endothelium characterized the glomerular lesions and as the process was acute no evidence of healing was seen in any of the lesions Davson Ball and Platt described a similar but not identical lesion in eight cases (their Group A) (64) There was patchy fibrinoid necrosis of the glomerular tufts but with varying amounts of epithelial crescent formation and partial fibrosis of the tufts Four similar cases were later added by Wainwright and Davson (297) Urinalysis is not helpful in differentiating the two diseases As has been shown by Schreiner (255) and Hamburger (107) even the telescoped urinary sediment may be found in both conditions and in other forms of glomerulonephriti In these circumstances can renal biopsy be of assistance in the differential diagnosis of SLE and polyarteritis nodosa?

The lesions described by Zeek as polyarteritis nodosa are obviously very different from those of SLE and their focal distribution and nature makes it unlikely that a positive diagnosis could be made in all cases by renal biopsy The necrotizing glomerulonephritis described by both the Cincinnati and the Manchester workers however is very similar to the glomerulonephritis seen in some cases of SLE and in one of her cases Zeek found some features of SLE (154) Patients with the necrotizing glomerulonephritis of hypersensitivity angiitis are acutely ill and the course is a rapid one In those patients with SLE and lupus nephritis who were acutely ill and in whom the clinical course was

vas

of

ve

difficulties involved in making an accurate histologic diagno is are u ted well in case 5 reported by Pagel and Treip (219) In this patient a 46 year old man the clinical diagnosis was either polyarteritis nodosa or SLE The patient died of rapidly progressive renal failure—a finding more in keeping with the diagnosis of hypersensitivity angiitis On the basis of the distinctive wire loop phenomenon Pagel and Treip concluded that the pathologic diagnosis was SLE no hematoxylin bodies were found We have shown that the wire loop lesion occurs in a variety of diseases and in patients with lupus nephritis running so fulminating a course hematoxylin bodies have been found in the areas of local necrosis (#28 30 32) as Smith (264) has also pointed out We conclude therefore that the diagnosis in Pagel s case was probably not SLE but Zeek hypersensitivity angiitis



Fig 37 *Kidney from a patient ill with long standing rheumatoid arthritis* (R&F Autopsy 68/1945) Note the diffuse hypercellularity of the glomerular tufts due to endothelial cell proliferation (H&E × 230) This type of diffuse glomerulitis resembles that observed in some instances of lupus nephritis (compare Fig 23)

3 RHEUMATOID ARTHRITIS

Joint pains and arthritis are prominent features of the symptomatology of SLE Mild arthritis is common but more severe degrees with marked deformities of the joints are unusual The kidneys are frequently affected in SLE but clinical involvement of the kidneys in rheumatoid arthritis is not significant Although few pathologic studies have been made in rheumatoid arthritis Cobb Anderson and Bauer (54) observed that renal disease was notably frequent Pirani and Bennett (225) found a proliferative glomerulitis in two of three cases (Fig 37) and Baggenstoss and Rosenberg (13) were impressed by a high incidence in autopsy material of a specific diffuse proliferative glomerulitis They speculated that the agent responsible for rheumatoid arthritis might also be responsible for a low grade subclinical glomerulitis (13) That this may be a terminal phenomenon is suggested by our own biopsy studies in twenty two patients with rheumatoid arthritis in none of whom were the glomeruli abnormal (230)

Rheumatoid arthritis is a generalized disease and on occasion needs to be differentiated from SLE Laboratory tests may afford little help in both diseases the globulins may be elevated the thymol turbidity and other flocculation tests may be positive (156 163 250) and Hargraves's cells may be found on examination of the bone marrow or peripheral blood (82 120 182 208 263) At the present time the exact relationship between the two diseases is a matter for speculation Hijmans and his colleagues (120) found Hargraves's cells in 54

of 455 cases (12%) of rheumatoid arthritis, and have suggested that some cases of rheumatoid arthritis may in fact be suffering from SLE

The following patient had rheumatoid arthritis for ten years before developing SLE and lupus nephritis:

Case 22

J.M (R & E 427706), a 47 year old laborer, had had intermittent attacks of conjunctivitis for 26 years In 1944 he first developed arthritis which involved symmetrically the interphalangeal, wrist elbow and ankle joints He was treated for rheumatoid arthritis Apart from recurrent attacks of arthritis resulting in some deformity he had no symptoms until the fall of 1954 when he complained of pleuritic pain and increasing shortness of breath In January, 1955, he developed a fever and was admitted to hospital acutely ill and anemic There was much edema of abdomen, sacral region and legs and he had ascites and bilateral pleural effusions The pulse was rapid, the blood pressure was 155/95 mm Hg the heart was enlarged a Grade III blowing systolic murmur was heard at the apex and there was electrocardiographic evidence of myocarditis Liver, spleen and lymph nodes were enlarged and on examination of the bone marrow many Hargraves's cells were found His condition improved rapidly after treatment with digitalis, low salt diet, and cortisone, but protein and hyaline casts were persistently found in the urine The maximum urinary specific gravity was 1 018, and the NPN was slightly elevated After leaving hospital on February 28 he was much improved, but still had intermittent chest pain and pains in the joints

In June 1955, he had a faint face rash, was anemic and the white cell count was low The

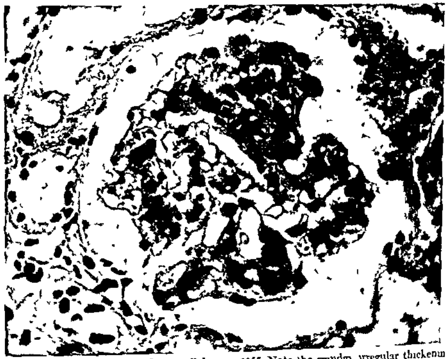


FIG 38 *Patient #22, First Biopsy, February 1955* Note the smudgy irregular thickening of the glomerular basement membrane This is strongly suggestive of fibrinoid In some areas there is obliteration of the capillaries, hypercellularity and slight karyorrhexis (early local necrotic lesion). (H&E × 500)

heart was slightly enlarged Liver spleen and lymph nodes were not palpable There was protein ++ in the urine, and many erythrocytes leucocytes and cellular, hyaline and fatty casts in the urinary sediment Tests of renal function were normal From July to November 1955 he had recurrent attacks of arthritis and purpura, was feverish, and had several small hemoptyses When admitted to hospital in November he was acutely ill feverish and complained of pain in the chest and in the joints There were many purpuric blotches on the skin of the arms and legs his legs were edematous the liver was enlarged the heart was enlarged and the blood pressure was 150/100 mm Hg The urine contained +++ protein and the microscopic urinalysis was unchanged His symptoms improved after the dose of prednisone was increased to 25 mg per day

Renal biopsies were made on February 28 June 16 and November 14 1955

The first renal biopsy (February 1955) (Fig 38) contained ten glomeruli their surrounding tubules and some medulla Most glomeruli were slightly ischemic and lobulated and there was a local irregular thickening of their basement membrane This was smudgy in character suggesting fibrinoid "Wire loop lesions were noted in a few places Mild local hypercellularity and occasional karyorrhexis were observed in a few glomeruli In these areas the capillary lumina were obliterated and a few adhesions between the tuft and Bowman's capsule were noted No 'hematoxylin bodies were seen The convoluted tubules were slightly dilated in places and there were distinct degenerative changes of their lining epithelium Proteinaceous material was present in Bowman's spaces and in the tubular lumina There was slight interstitial edema and fibrosis and a small number of chronic inflammatory cells infiltrated the interstitial tissue

Diagnosis Local and generalized membranous glomerulonephritis

Second Renal Biopsy (June 1955) (Fig 39) Five glomeruli with their surrounding



Fig 39 *Patient #22 Second Biopsy, June 1955* In both glomeruli note the irregular smudgy thickening of the basement membrane It is local in the glomerulus on the left, diffuse in that on the right. A well organized adhesion can be seen between the glomerular tuft and Bowman's capsule in the glomerulus on the right, this is probably the end result of local necrosis in this area There is a moderate degree of interstitial edema and tubular degeneration. (H&E × 350)

tubules were included in the sections The glomeruli were ischemic and somewhat lobulated There was a rather marked local thickening of the basement membrane which was smudgy and granular in places suggesting fibrinoid In places this thickening was quite marked with obliteration of the capillary lumina There were adhesions between the glomerular tufts and Bowman's capsule There was minimal local hypercellularity, and occasional karyorrhexis in these areas Abundant proteinaceous material was found in Bowman's spaces and in the lumina of the convoluted tubules which were dilated in some places and atrophic in others The tubules were lined by a low cuboidal epithelium in which distinct degenerative changes were seen A few tubules were completely filled by pale bluish homogeneous casts which stained strongly positive with the PAS technique There was edema and fibrosis of the interstitial tissue which was infiltrated by a small number of chronic inflammatory cells The changes were more severe than in the first biopsy

Diagnosis Local and generalized membranous glomerulonephritis

Third Renal Biopsy (November 1955) (Fig 40) Twelve glomeruli their surrounding convoluted tubules and a little medulla were included in the sections There was irregular local thickening of the basement membrane of all glomeruli It was smudgy and granular in appearance resembling fibrinoid, occasional 'wire loops' were seen In some glomeruli the capillary loops had coalesced in areas and were necrotic, fibrinoid material nuclear

casts There were moderate degenerative changes in the tubular epithelium There was much



Fig 40 *Patient #22, Third Biopsy November 1955* Note a typical lesion of local necrosis with adhesions to Bowman's capsule Within this area note the smudgy fibrinoid material "Hematoxylin" bodies are present but cannot be clearly seen in this black and white photomicrograph In the remainder of the glomerulus slight thickening of the basement membrane is evident Bowman's space contains proteinaceous material Note the vacuolar degeneration of an adjacent convoluted tubule (H&E × 500)

patchy fibrosis of the interstitial tissue which was infiltrated with a moderate number of chronic inflammatory cells There was mild thickening and sclerosis of the walls of the small arteries and arterioles in some there were changes suggestive of fibrinoid These findings were confirmed in Mallory and PAS preparations The lesions were more marked than in the second biopsy

Diagnosis Local and generalized membranous glomerulonephritis diagnostic of lupus nephritis

4 SCLERODERMA AND DERMATOMYOSITIS

According to Klemperer the morphologic evidence permits the conclusion that generalized scleroderma (progressive diffuse sclerosis) is characterized anatomically by a fundamental implication of collagenous tissues (144) The sclerotic process can be traced to the connective tissue framework of the organs and appears to be the result of an increase in collagen fiber formation despite widespread hyperplasia of the connective tissue fibers there is no concomitant fibroblastic activity in any phase of the morbid process (148) Nevertheless fibrinoid alterations have been observed in association with the progressive sclerotic transformation of the collagenous tissues and as Moore and Sheehan (195) have shown both changes are commonly found together in the kidney Klemperer himself points out that the sclerosing change observed in scleroderma is not specific to that disease and is a common finding in the spleen pericardium and retroperitoneal tissues of patients with SLE (152) Thus it is not surprising on morphologic grounds to find that in some patients there may be no clear cut differences between SLE and scleroderma and that rigid classification may be impossible Recently Richards (243) reported a patient in whom the clinical features were those of SLE but who had scleroderma of the fingers and Tumulty (290) also mentioned skin changes resembling those of scleroderma in patients ill with SLE This problem also arose in the case reported by Volpe and Hauch (294) Their patient diagnosed by them as suffering from scleroderma was diagnosed elsewhere as SLE when many Hargraves s cells were repeatedly found on examination of the bone marrow From the clinical history it is perhaps more likely that the patient was suffering from SLE Surely we can admit that she presented features of both illnesses We encountered a similar problem in one of our patients

Case

In 19 0 M T (I C F 44011) a light skinned emotional 39 year old negro housewife noticed migratory joint pains affecting the interphalangeal shoulder and knee joints Two years later she suffered from malaise and anorexia and complained of shortness of breath All lymph nodes were enlarged and on study of a lymph node biopsy hyperplastic lymphadenitis was found

In July 1953 a butterfly face rash appeared after exposure to the sun She ran a low grade fever and edema of the face and pretibial regions was noted The lymph nodes and liver were now enlarged The patient was anemic had a pericardial effusion and the serum globulin level and ESR were raised Hargraves s cells were not found on examination of the bone marrow but a biopsy from the skin of the face was considered to be compatible with lupus erythematosus When she was treated with cortisone her symptoms improved considerably

Following this however she continued to have intermittent joint pains and recurrent pleural pain was troublesome She lost much hair from the scalp

When seen again in July 1954 there was atrophy of the skin in patches in the butterfly area of the face The lymph nodes were enlarged and a pericardial effusion was found The thymol turbidity was 12 units and Hargraves s cells were found in the peripheral blood At this time however a new and striking feature had appeared The skin of the forearms and of the fingers was tense shiny atrophic and indurated and multiple paronychiae were prominent A skin biopsy revealed dermal fibrosis

By August 1955 she had become very weak and fatigued easily and she had developed severe Raynaud s phenomenon The skin had become thick and indurated Areas over the hands were white and tender and the skin was firmly bound down The liver was enlarged and tender and tests of liver function were abnormal Hargraves s cells were repeatedly found in the peripheral blood On barium swallow severe esophageal changes typical of scleroderma were seen A skin biopsy showed changes characteristic of scleroderma Renal biopsies made in October 1953 September 1954 and August 1955 were reported as essentially normal

The initial diagnosis in this patient was SLE This was made because of the intermittent febrile course, the development of a typical face rash the affection of lymph nodes and liver, and of the joints pleura and pericardium The serum globulin and thymol turbidity were raised the skin biopsy was consistent with *the diagnosis and Hargraves s cells were repeatedly found And yet at a later* stage findings typical of scleroderma were noted We are driven to conclude that this patient suffers from a diffuse collagen disorder with features of both SLE and scleroderma

The pathology of the kidneys in generalized scleroderma was described by Masugi and Ya Shu in 1938 who were the first to point out that extensive fibrinoid changes could occur in the connective tissues of the arterioles and glomeruli (179) Two years later, Pollack described two cases of scleroderma with extensive fibrinoid changes in the vessels (228) both had severe renal involvement and in one the lesions resembled those seen in SLE In his discussion of Pollack s paper Baehr stated that both patients had a long *intermittent febrile* course persistent hematuria involvement of the synovial membranes of the joints and involvement of pleura pericardium and peritoneum Leucopenia and depression of the hemoglobin were found in one On the other hand as a result of their experience of 150 cases of scleroderma Leinwand *et al* (165) have pointed out that hematuria does not occur for long periods and usually develops only in the terminal stage of the illness whereas one of our patients (#23) with SLE had prolonged hematuria for about one year Thus despite the typical skin lesion the clinical course of the patients described by Pollack more closely resembled that of SLE than that of scleroderma and it is probable that they had features of both diseases

The cl

sclerodern

evidence

velops ab

195 244) The pathology of the renal lesion has been described by Masugi and Ya Shu (179), Bevans (27) Goetz (94), Moore and Sheehan (196), Leinwand

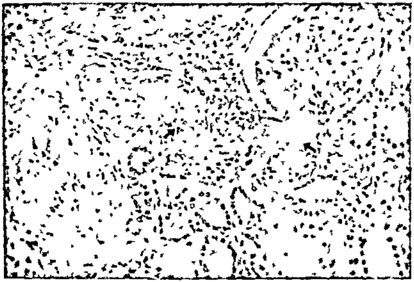


Fig 41 *Kidney from a patient with scleroderma who died with severe and rapidly progressive renal failure* (R&E Autopsy 135 1956) Note the marked intimal thickening in the small artery on the left and almost complete obliteration of the lumen The mucinous-like character of this thickening is not clearly demonstrated in this black and white photomicrograph Distinct fibrinoid changes are seen in the thickened wall of the arteriole (arrows center and right) leading into the glomerulus Note also the diffuse thickening of the basement membrane in the glomerulus (H&E × 150)

(165), and recently by Rodnan and his colleagues (244) The lesion affects the origins of the intralobular arteries, where a concentric mucinous like thickening of the intima may be so severe as to stretch the media of the vessel (Fig 41) When severe these lesions result in a widespread focal cortical infarction which gives the lesion its patchy character Fibrinoid necrosis is often seen at the peripheral portion of the intralobular arteries and may extend distally from there into the glomerular tufts (Fig 41) As not all arteries are affected the lesion is patchy in its distribution and areas of normal kidney are found between areas which are grossly damaged Moore and Sheehan rightly observe that this lesion differs from that seen in the other so called collagen diseases

Dermatomyositis has been considered by some authors to be akin to scleroderma but others have regarded the two diseases as distinct clinical entities (65) In 1940 Keil described in detail five cases which he considered showed transitional features between dermatomyositis and SLE (138) These patients all had long and complicated clinical histories but despite the completeness of the protocols it is impossible to be certain that any of them was suffering from SLE Postmortem examinations in two of them did not reveal any lesions diagnostic of SLE

Renal disease has rarely been reported in dermatomyositis Talbott and his colleagues reported a single case in 1939 (282) Originally the diagnosis was

scleroderma and a skin biopsy had shown features "similar to those observed *in some cases of muscular weakness associated with arthritis and scleroderma*." In the last week before this patient's demise there occurred a sudden deterioration in renal function—which had previously been normal. The postmortem diagnosis was "chronic diffuse dermatomyositis with scleroderma." The authors commented on the renal lesion as being in their experience, unique. There was a widespread focal cortical infarction, but the glomeruli within these degenerating areas were preserved. The medullary and arcuate branches of the renal artery were normal, but the intralobular arteries showed an infiltration *of their subintimal substance* by a mucinous material; these lesions ceased abruptly when the vessels assumed the caliber of afferent arterioles. Fibrinoid necrosis was seen in a few arteries. This renal lesion resembles very closely that described later in scleroderma, both clinically and pathologically (165, 195, 244), and cannot be considered to be due to dermatomyositis *per se*. Keil reviewed the published cases of dermatomyositis (139) and concluded that "the kidneys are, as a rule, spared in dermatomyositis," although he himself had referred to the rare occurrence of gross hematuria, azotemia and hypertension. *Recently Domzalski and Morgan were unable to adduce any further evidence* of kidney involvement in dermatomyositis (65).

5. THROMBOTIC THROMBOCYTOPENIC PURPURA

[illegible]

outcome within at most eight weeks (262). The clinical picture is usually episodic *and is characterized by thrombocytopenic purpura*, severe hemolytic anemia and bizarre and transitory neurologic signs. These clinical findings may also occur as manifestations of SLE.

Thrombotic thrombocytopenic purpura is sometimes associated *with other so*-called collagen diseases (262), and a number of cases have been reported in which there were features of thrombotic thrombocytopenic purpura and of SLE (17, 18, 46, 161, 279, 280, 299). The following case was diagnosed clinically as suffering from SLE. At the postmortem examination *lesions of both SLE* and thrombotic thrombocytopenic purpura were found.

R.S. (R & E 40,015), a 31 year old television repair man, had had diabetes mellitus since 1950. Nevertheless his health was good until 1952 when swelling of the joints of his fingers occurred. Thenceforward he had intermittent attacks of pain and swelling involving the fingers, wrists, elbows, knees and ankles. In May 1953 he had a thrombophlebitis of the right leg. One year later a diagnosis of rheumatoid arthritis was made when pain and swelling of the joints recurred. Because he had attacks of severe pleuritic pain *and the* Wassermann reaction was positive the diagnosis of SLE was considered, but Hargraves's cells were not found.

Subsequently he had episodes *of fever and lethargy*. *In* October 1955 he had chills, was feverish and complained of severe generalized abdominal pain which persisted until his admission to hospital on November 14, 1955. He was acutely ill, his temperature was 104° *and the pulse rate was 120 per minute* with multiple extrasystoles. There was a generalized

lymphadenopathy and bilateral pleural effusions petechiae were found in the mouth and on the skin of the chest and abdomen There was generalized abdominal tenderness and marked rebound tenderness but bowel sounds were present The urine specific gravity was 1 031, the urine contained protein ++ no bile and a trace of urobilinogen In the urinary sediment there were many erythrocytes 20-30 leucocytes some of which were in clumps many hyaline and granular and a few leucocyte casts The hematocrit was 30% the leucocyte count was 2200/mm^3, and adequate numbers of platelets were seen on a blood smear The serum bilirubin was 0.29 mg/100 ml serum albumin 3 1 gm/100 ml, serum globulin 2 0 gm/100 ml (gamma globulin 1 05 gm/100 ml) He was diagnosed as having an acute exacerbation of SLE with acute abdominal complications of lupus (229) and was therefore treated with intravenous hydrocortisone 500 mg daily later as his condition improved he was given hydrocortisone by mouth Blood cultures and the Wassermann reaction were negative The leucocyte count was persistently low Later he developed a pericardial friction rub and a systolic murmer was heard at the base of the heart In March 1956 he complained of severe headaches subsequently became comatose had several clonic convulsions and died He did not have purpura at this time

At the postmortem examination a verrucal nonbacterial endocarditis of the mitral valve was found There was moderate hypertrophy of the left ventricle bilateral adhesive pleuritis and acute bronchopneumonia There were multiple widespread platelet thrombi in the arterioles of myocardium lung brain spleen liver and kidneys There was generalized lymph node hyperplasia and moderate splenomegaly Well marked periarterial fibrosis was seen in the spleen (Fig 42) In the kidneys (Fig 43) the basement membrane of most glomeruli was irregularly thickened the thickening was severe in areas resulting in marked narrowing of the capillary lumina In places the thickened basement membrane appeared smudgy and granular suggesting the presence of fibrinoid Wire loop lesions were seen in some glomeruli There was no cellular proliferation in the glomeruli The convoluted tubules were atrophic in areas and degenerative changes were seen in the lining epithelium

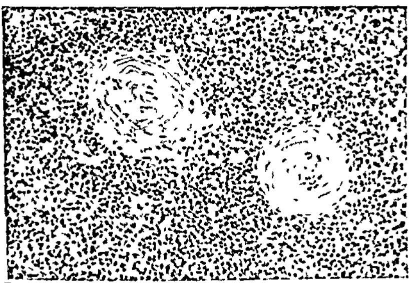


Fig 42 *Patient, R S Autopsy Spleen from a patient who died of SLE and thrombotic thrombocytopenic purpura* Note the laminated periarterial fibrosis in the penicillar arteries This is typical of SLE Note that a small subendothelial platelet thrombus can be seen in the artery on the left (H&E × 170)



FIG 43 *Patient R S Autopsy Kidney from a patient who died of SLE and thrombotic thrombocytopenic purpura* Note the severe and diffuse somewhat smudgy thickening of the glomerular basement membrane and the wire loop lesions To the right of the glomerulus *a small artery is completely occluded by a fairly homogeneous platelet thrombus* (H&E × 230)

There was considerable fibrosis of the interstitial tissue in places and infiltration with chronic inflammatory cells A moderate degree of thickening and hyalinization of the walls of the small arteries and arterioles was noted The lumina of many were almost completely occluded by irregular smudgy eosinophilic thrombi—some of which were undergoing organization

Diagnosis Diffuse and generalized membranous glomerulonephritis consistent with lupus nephritis Multiple arteriolar platelet thrombi

A clinical diagnosis of SLE was made because the patient had a prolonged episodic illness with fever, malaise, arthritis, and evidence of involvement of pleura pericardium and peritoneum The leucocyte count was persistently low, the Wassermann reaction was positive transiently, and the findings in the urinary sediment were consistent with the diagnosis of SLE At the postmortem examination a pathologic diagnosis of SLE was made because there was periarterial fibrosis of the spleen, verrucous nonbacterial endocarditis, and the renal lesions were compatible with lupus nephritis Save for the terminal episode of coma and convulsions there was no clinical evidence to suggest thrombotic thrombocytopenic purpura, yet arteriolar platelet thrombi were found postmortem widespread throughout the organs A similar case with Hargraves's cells in the peripheral blood and clinical and pathologic features of SLE and thrombotic thrombocytopenic purpura was reported recently by Laszlo, Alvarez and Friedman (161)

Six years ago the opinion was expressed that the lesions of thrombotic thrombocytopenic purpura were "entirely different from those of periarteritis nodosa, disseminated lupus erythematosus and of the usual infectious diseases" (43). Orbison considered it to be a variant of one of the previously characterized collagen diseases stating that "This stand is supported by the prominent aneurysms, large occlusive masses in the arteries and capillaries and the focal destructive lesions of the arteries which characterize this disease are not found in other members of the group [of collagen diseases]" (212). Nonetheless features of SLE or of polyarteritis nodosa have been found in ten percent of the reported cases of thrombotic thrombocytopenic purpura (262) and in one instance features of all three were noted (280). The exact nature of thrombotic thrombocytopenic purpura and its relationship to the other collagen diseases needs clarification.

Capillary and arteriolar damage may be widespread in both SLE and thrombotic thrombocytopenic purpura. Several observers have presented evidence that the vascular damage actually precedes the formation of platelet thrombi in thrombotic thrombocytopenic purpura (6, 99, 212). In our opinion it would seem possible that widespread platelet thrombosis with or without thrombocytopenia and purpura might occur as a complication of the vascular damage in SLE. It is surprising that it is not seen more frequently.

The kidneys are affected often in thrombotic thrombocytopenic purpura. The urine usually contains small amounts of protein; gross or microscopic hematuria and granular casts are frequently found; renal insufficiency and moderate azotemia are quite common (262). Thus examination of the urinary sediment is not helpful in differentiating this condition from lupus nephritis. The differential histologic diagnosis usually presents little difficulty. Eosinophilic thrombi apparently consisting only of fibrin and platelets are found in the arterioles and locally within the glomerular capillaries. In the typical case of thrombotic thrombocytopenic purpura glomerular changes are limited to the areas immediately adjacent to the capillary thrombi and the remainder of the involved glomeruli is normal (10, 262). In contrast with lupus nephritis the only glomeruli affected are those in which the capillaries or arterioles contain platelet thrombi; a large proportion of glomeruli is normal. There are several reports of various forms of nephritis in cases dying of thrombotic thrombocytopenic purpura (60, 99, 204, 299); it is not clear from these reports whether or not the simultaneous occurrence of nephritis and of thrombotic thrombocytopenic purpura in these patients was fortuitous.

6. SARCOIDOSIS AND WEGENER'S GRANULOMATOSIS

Before Keil's masterly analysis (136) showing that the simultaneous occurrence of SLE and tuberculosis was fortuitous, it was assumed, especially in France and in Vienna, that the two diseases were related intimately, and that tuberculosis was the cause of death in patients ill with SLE.

The association of cutaneous sarcoidosis and lupus erythematosus has been reported and proven histologically in four patients (93, 189, 275). In recent

years Teilum has advanced the opinion that there is a definite association between non tuberculous granulomatous lesions and systemic lupus erythematosus He first described two cases in 1945 (283) In our opinion the findings given in the protocol of the second case are insufficient to warrant a definitive diagnosis of SLE The first case, a twenty year old girl, had all the clinical features of SLE At the postmortem examination the kidney lesions were *compatible with lupus nephritis, and periarterial fibrosis was noted in the* spleen (286) In the lungs multiple nodular subserous giant cell granulomata were found there was a focal fibrinoid necrotizing process in the interstitial connective tissue and in the walls of vessels, both in the lungs and the lymph nodes No Schaumann bodies were found in the granulomatous lesions In a later paper Teilum *concluded that the miliary epithelioid cell granulomata* in the serosa together with focal necrotizing and granulomatous processes have to be interpreted as tissue injury specific to the disease [SLE] (284) His pathologic findings have not been confirmed either by ourselves or by numerous other investigators

Teilum also considered that the hyperglobulinemia periarterial fibrosis of the spleen and wire loop lesions of the glomeruli in SLE were expressive of a primary allergic hyperglobulinosis in the reticulo endothelial system analogous to *the morphologic immunity reaction in Boeck's sarcoid (286)* In our opinion the clinical and pathologic similarities between the two diseases are at best superficial Despite the relative frequency of SLE and sarcoidosis their simultaneous occurrence in the same patient is so rare that it should be considered fortuitous Recently we have studied by serial renal biopsies two *patients in whom it seemed possible at first that the two diseases* might be associated In the first patient the clinical features of SLE were observed Hargraves's cells were found and the kidney lesions were diagnostic of lupus nephritis The granulomatous lesions were at first thought to be due to sarcoidosis but were later shown to be due to tuberculosis The second patient had widespread granulomatous lesions for two years and a diagnosis of sarcoidosis was made by lymph node biopsy He developed the nephrotic syndrome, and at the first biopsy renal lesions suggestive but not diagnostic of lupus nephritis were found *Subsequently he has been observed for twelve months* and no other clinical or biochemical features have suggested the diagnosis of SLE Thus we can assume that neither patient had both SLE and sarcoidosis Renal involve ... due

from that of lupus nephritis

In Wegener's granulomatosis the lungs and upper respiratory passages are involved by necrotizing giant *cell granulomas (77 91 164)* Sooner or later in most patients evidence of renal damage appears and about one half of the reported cases hav

almo t invariably

involved by this pr

of capillary loops and scanty polymorphonuclear cell exudation ...

lesion is similar to the local necrotic lesion seen in lupus nephritis However, in Wegener's granulomatosis more glomeruli are involved, "hematoxylin" bodies are not seen, and granulomatous lesions are found in the interstitial tissue (91) The lesions in the lungs and in other organs bear no morphologic resemblance to those of SLE

XI THE NATURAL HISTORY OF LUPUS NEPHRITIS

Lupus nephritis is a progressive fatal glomerulonephritis, which at present, is the main cause of death and the most serious problem in patients ill with SLE In lupus nephritis the glomerular tuft is damaged, and reacts to deposits of abnormal mucopolysaccharides and other proteinaceous substances, with the appearance of local basement membrane thickening 'fibrinoid change,' hematoxylin" bodies and endothelial cell proliferation At any moment in time the kidneys of two thirds of patients ill with SLE are involved to a greater or lesser degree by these pathologic abnormalities and their consequences The majority of patients ill with SLE die of renal failure and lupus nephritis is found on post mortem examination in over 75 percent Its course may be fulminating and the patient may die of renal failure within weeks of the clinical onset of the illness On the other hand lupus nephritis may develop slowly in a patient who has been ill with SLE for months or years or may present with the gradual onset of a classical nephrotic syndrome—which may be the only overt manifestation of SLE Usually it progresses slowly but inexorably to death during a period of about one to four years A small proportion of patients may live longer In general the rate of progression of lupus nephritis is more rapid than that seen in the common forms of glomerulonephritis related to streptococcal illness

The earliest lesion of lupus nephritis consists of a local membranous glomerulitis involving small areas at the periphery of the glomerular tuft Small areas of endothelial cell proliferation are also commonly seen These early lesions have been found by renal biopsy in the absence of signs symptoms or laboratory data indicating involvement of the kidney The urine may be normal or it may contain protein leucocytes in clumps and leucocyte casts—a finding which often leads to the erroneous diagnosis of pyelonephritis* At this stage of the illness tests of renal function are of little value in making a diagnosis Renal involvement which can only be suspected clinically may be diagnosed by renal biopsy

The rate of development of the glomerular changes and the progress of the renal disease may depend on the extent and severity of the initial lesions in the kidney The progression of the lesion in the glomerulus is indicated by the appearance or increase of fibrinoid material in the basement membrane by an increase in proliferative lesions by the development of adhesions between the tuft and Bowman's capsule and in some cases by the development of local areas of necrosis and karyorrhexis These lesions may mimic the embolic glomerulonephritis of Lohlein

As the renal lesion progresses erythrocytes and granular casts appear in the

*Many patients with acute SLE develop transitory urinary abnormalities and a rise in the blood non protein nitrogen These patients do not necessarily have lupus nephritis This can only be diagnosed clinically when the urinary abnormalities persist

urine of most patients, and epithelial cell casts fatty casts and oval fat bodies in the urine of some renal function decreases azotemia increases, and the clinical manifestations of renal involvement such as *nocturia polyuria and thirst* make their appearance From our experience we suspect that—if they live long enough—almost all patients with progressive lupus nephritis will pass through an edematous stage of *nephritis associated with hypoalbuminemia hypercholes*terolemia and much proteinuria When this nephrotic syndrome appears the typical face rash of SLE may have disappeared and is usually absent once severe *renal disease is established In other patients ill with SLE* as we have mentioned above the nephrotic syndrome may be the presenting manifestation of the disease The diagnosis of SLE may be overlooked because the better known *symptoms* and *signs* of SLE may be absent or minimal when edema develops Usually a carefully taken history establishes the presence of symptoms of SLE in the immediate or remote past Presumably lupus nephritis is the cause of the nephrotic syndrome in adults in a significant proportion of cases and the exact diagnosis is best made by finding the characteristic histologic picture by renal biopsy

In this form of the nephrotic syndrome spontaneous or induced diuresis with rapid clearing of water logging is not commonly seen and the edema usually persists for months Usually the patient s disease slides imperceptibly from the edematous phase into a slowly or more rapidly progressive chronic renal failure During the edematous phase there may be histologic evidence of either membranous or membranous and proliferative changes in the glomerular tuft and epithelial crescents may be found The features more peculiar to lupus nephritis are usually present at this stage Tubular degeneration is evident and fatty changes are demonstrable with special stains Interstitial edema and mild fibrosis are common and the vessels of the kidney may contain fibrinoid At this stage of the illness the kidney may be prone to infection and secondary involvement with inflammatory diseases such as pyelonephritis may be evident clinically and histologically Progression to chronic glomerulonephritis with contraction of the kidney is rare and hyalinization of the glomeruli is unusual Th... t... les become atrophic or dilated but severe tubular atrophy is rare

hill *Proteinuria decreases* and casts appear in increasi...
Th... tests of renal function become most abnormal Clinical and laboratory

or during an acute exacerbation of SLE with ...
or ne...olog...cal crises Usually death is in chronic renal failure and in many
... of any

the end the kidney may be indistinguish...

chronic glomerulonephritis of the common type and microscopically little or no evidence of the lesions typical of lupus nephritis may be found

One other facet of lupus nephritis remains to be discussed In a few cases the disease may run a fulminating course (pseudo nephrotic syndrome) The glomeruli are severely damaged from the outset Although a brief history of other symptoms of SLE may be elicited the onset may be sudden The patient is admitted with much protein in the urine and appears to have the nephrotic syndrome However the serum cholesterol level is low In our experience this pseudo nephrotic picture was usually complicated by the development of other evidence of acute SLE such as abdominal crises and myocarditis After a short stormy illness the patient dies in renal failure The cause in not difficult to find Renal function has been compromised by a most extensive and active glomerular disease in which widespread local necrosis fibrinoid change, karyorrhexis, 'hematoxylin bodies and hyaline thrombi occupy the stage Severe tubular damage and interstitial edema fibrosis and inflammation complete the picture

ACKNOWLEDGMENTS

We would like to thank Dr James A Schoenberger for doing the tests of discrete renal function on six of our patients Dr George Hass Dr Cecil A Krakower, and Dr Hans Popper for access to material in their Departments of Pathology Dr R A Clasen Dr Edwin Irons Dr Peter Pulos and Dr Charles Wolfe for their interest and help

We would like to thank Miss Loretta Cudnowski and Miss Joan Halle for their untiring help with the nursing of these patients Mr Jackson Lucas, Mrs Myrtle Petrunkewitch Mrs Polacek Miss Dolores Rix and the late Mrs Florence Ross for technical assistance

Mrs Ruth Best and Mr Lawrence Toriello of the Illustration Studios University of Illinois made the charts and photomicrographs

We are indebted to the Upjohn Company Kalamazoo Michigan for arranging for the publication of the color plates In particular we would like to thank Dr A G MacLeod and Miss Helen Burrell for their help

The prednisone used in the later part of this study was kindly supplied as Meticorten® by Dr George Babcock Jr of the Schering Corporation Bloomfield, New Jersey

BIBLIOGRAPHY

1 Addis T A clinical classification of Bright's Disease J A M A 85 163 1925
2 Addis T Glomerular nephritis Diagnosis and treatment New York The MacMillan Company 1952
3 Allen A C The Kidney Medical and Surgical Diseases New York Grune & Stratton 1951
4 Allen A C Clinicopathologic meaning of the nephrotic syndrome Am J Med 18: 277 1955
5 Angevine D M Structure and function of normal connective tissue Transactions of First Conference on Connective Tissues J Macy Jr Foundation 13 1950

6 ALTSCHULE M D A rare type of acute thrombocytopenic purpura Widespread formation of platelet thrombi in capillaries New England J Med 227 477 1942
7 ALTSCHULER C H AND ANGEVINE D M Histochemical studies on the pathogenesis of fibrinoid Am J Path 25 1061 1949
8 BAEHR G Renal complications of endocarditis Tr A Am Physicians 46 87 1931
9 BAEHR G KLEMPERER P AND SCHIFRIN A A diffuse disease of the peripheral circulation (usually associated with lupus erythematosus and endocarditis) Tr A Am Physicians 50 139 1935
10 BAEHR G KLEMPERER P AND SCHIFRIN A An acute febrile anemia and thrombocytopenic purpura with diffuse platelet thromboses of capillaries and arterioles Tr A Am Physicians 51 43 1936
11 BAEHR G AND POLLACK A D Disseminated lupus erythematosus and diffuse scleroderma J A M A 134 1169 1947
12 BAGGENSTOSS A H Visceral lesions in disseminated lupus erythematosus Proc Staff Meet Mayo Clin 27: 412 1952
13 BAGGENSTOSS A H AND ROSENBERG E F Visceral lesions associated with chronic infectious (rheumatoid) arthritis Arch Path 35 503 1943
1

15 BARBER H W A case of acute lupus erythematosus Brit J Dermat 27 365 1915
16 BARBER H W Lupus erythematosus associated with streptococcal infection of the tonsil Brit J Dermat 31 156 1919
17 BARONDESS J A Thrombotic thrombocytopenic purpura Review of the literature and report of three cases Am J Med 13 294 1952
18 BEIGELMAN P M Variants of the platelet thrombosis syndrome and their relationship to disseminated lupus A M A Arch Path 51 213 1951
19 BELL E T Renal Diseases Ed 2 Philadelphia Lea and Febiger 1950
2 [illegible] Dermat [illegible]

s relation

22 BEN ASHER S Recurrent acute lupus erythematosus [illegible] of a case which has survived 23 years after onset of systemic manifestations Ann Int Med 34 243 1951
[illegible] of the effect of [illegible] cular lesions 88: 197 1951

24 B[illegible]

25 BERMAN L AXELROD A R GOODMAN H L AND [illegible] erythematosus [illegible] phenomenon of bone marrow and blood Am J Clin Path 20 403 1950
26 BEVANS M Pathology of scleroderma with special reference to the changes in the gastro intestinal tract Am J Path 21 25 1945
27 BIETT T quoted in Abrégé pratique des maladies de la peau by Cazenave A and Schedel H E Paris 1828 p 386
28 BJØRNEBOE M BRUN C GORMSEN H IVERSEN P AND RAASCHOU F The nephrotic syndrome II The effect of corticotrophin (ACTH) Acta Med Scandinav Supp 266: 219 1952
29 BLANKENHORN M A AND KNOWLES H C Periarteritis nodosa recognition and [illegible] Int Med 41 887 1954

31 BOLLET A J, SEGAL, S, AND BUNIM J J Treatment of systemic lupus erythematosus with prednisone and prednisolone J A M A 159: 1501, 1955
32 BOOTH, E, MUIRHEAD, E E, AND MONTGOMERY P O B The fibrinoid of renal cortical necrosis due to the Shwartzman reaction Evidence for its origin from smooth muscle A M A Arch Path 61 169 1956
33 BORSAK F T, AND ADLERSBERG D The nephrotic syndrome attempt at classification by clinical and biochemical criteria Clin Res Proc 3: 139 1955
34 BOYD W A Textbook of Pathology Philadelphia, Lea and Febiger 1953
35 BRENNER J J JAFFE W A AND HOCHSTEIN E Lupus erythematosus disseminatus sine lupo with the nephrotic syndrome Am J Med 5 288 1948
36 BROOKE H G Lupus erythematosus and tuberculosis Brit J Dermat 7 72 1895
37 BROWN T McP WICHELHAUSEN R H MERCHANT W R AND ROBINSON L B Antigen-antibody mechanism in rheumatic diseases Am J Med Sci 221 618 1951
38 BRUNSON J G, AND DAVIS R L Systemic fibrinoid diseases Arch Path 60 593 1955
39 BRUNSON J G, GAMBLE C N AND THOMAS L Morphologic changes in rabbits following the intravenous administration of meningococcal toxin I The effects produced in young and in mature animals by a single injection Am J Path 31: 489 1955
40 BRUNSON J G THOMAS L AND GAMBLE C N Morphologic changes in rabbits following the intravenous administration of meningococcal toxin II Two appropriately spaced injections the role of fibrinoid in the generalized Shwartzman reaction Am J Path, 31. 655 1955
41 BRUNSTING L A Systemic lupus erythematosus S Dakota J Med 7 311 1954
42 BRUNSTING L A SLOCUMB C H AND DIDCOCT J W Effects of cortisone in acute disseminated lupus erythematosus A M A Arch Dermat & Syph 63 29 1951
43 P W C Editorial Thrombotic thrombocytopenic purpura Ann Int Med 33 739 1950
44 CANTAROW A AND TRUMPER M Clinical Biochemistry Ed 5 Philadelphia W B Saunders Co 1955
45 CAREY R A HARVEY A M AND HOWARD J E The effect of adrenocorticotropic hormone (ACTH) and cortisone on the course of disseminated lupus erythematosus and periarteritis nodosa Bull Johns Hopkins Hosp 87 425 1950
46 Case records of the Massachusetts General Hospital Case 38301 New England J Med 247 133 1952
47 CAVAFY J Case report to Dermatological Society of London Brit J Dermat 9 328 1897
48 CAZENAVE A Annales des Maladies de la Peau 3 298 1851 Quoted by Ormsby O S and Montgomery H Diseases of the Skin Ed 7 Philadelphia Lea and Febiger 1948
49 CAZENAVE A AND CHAUSIT J M Traite Elementaire des Maladies de la Peau 8th ed Paris Bailliere 1853
50 CAZENAVE A AND SCHEDEL H E Abrege Pratique des Maladies de la Peau 3rd ed Paris 1838
51 CHURG J, AND GRISHMAN E Phase microscope studies of renal glomeruli—glomerular deposits of hyaline substances Am J Path 29 199 1953
52 CITRON K M Renal impairment in sarcoidosis with special reference to nephrocalcinosis Postgrad Med J 31 516 1955
53 CIVATTE A Les recherches sur l'etiologie du lupus erythemateux depuis 20 ans Ann d Dermat et Syph 7 465 1926
54 COBB S ANDERSON F AND BAUER W Length of life and cause of death in rheumatoid arthritis Ann Rheum Dis 12 323 1953
55 COHEN H AND CADMAN E F B The natural history of lupus erythematosus and its modification by cortisone and corticotrophin (A C T H) Lancet 2: 305 1953
56 COLE L R Periarteritis nodosa Report of a case with characteristic urinary sediment J.A M.A 149 1619 1952
57 COMENS, P Experimental hydralazine disease and its similarity to disseminated lupus erythematosus J Lab and Clin Med 47: 444 1956

58 CONWAY, E J Microdiffusion Analysis and Volumetric Error London, Crosby Lockwood & Son Ltd, 1950
59 COOMBS, R R A, MOURANT, A E, AND RACE, R R · New test for detection of weak and "incomplete" Rh agglutinins Lancet, 2: 15, 1945
60 COOPER, T, STICKNEY, J M, PEASE, G L, AND BENNETT, W. A · Thrombotic thrombocytopenic purpura Confirmation of clinical diagnosis by bone marrow aspiration Am J Med, 13 374 1952
61 CROCKER, H R Diseases of the Skin Ed 3, Philadelphia, Blakiston, 1903
62 DAMMIN, G J, NORA, J R, AND REARDAN, B Hydralazine reaction Case with LE cells antemortem and postmortem, and pulmonary, renal, splenic and muscular lesions of disseminated lupus erythematosus J Lab & Clin Med, 46 806, 1955
63 DAUGHERTY, G W, AND BAGGENSTOSS A H Syndrome characterized by glomerulonephritis and arthritis Libman-Sacks disease with predominately renal involvement Arch Int Med, 85· 900 1950
64 DAVSON J, BALL, J, AND PLATT, R The kidney in periarteritis nodosa Quart J Med, 17· 175 1948
65 DOWZALSKI, C A, AND MORGAN, V C · Dermatomyositis diagnostic features and therapeutic pitfalls Am J Med, 19. 370 1955
66 DUBOIS E L The effect of the LE cell test on the clinical picture of systemic lupus erythematosus Ann Int Med, 38 1265, 1953
67 DUBOIS E L, COMMONS, R R, STARR, P, STEIN, C S, JR, AND MORRISON, R Corticotropin and cortisone treatment for systemic lupus erythematosus J.A.M.A 149 995, 1952
68 DUSTAN, H P, TAYLOR R D, CORCORAN, A C, AND PAGE, I H Rheumatic and febrile syndome during prolonged hydralazine treatment J.A M A, 154· 23 1954
69 EHRICH, W E Nature of the collagen diseases Am Heart J, 43: 121, 1952
70 EHRMANN S AND FALKENSTEIN, F Uber lupus erythematodes Arch f Dermat u Syph 141. 408 1922
71 ELKINTON, J R, HUNT, A D, JR, GODFREY, L McCRORY, W W, ROGERSON, A G, AND STOKES, J, JR Effects of pituitary adrenocorticotropic hormone (ACTH) therapy, J.A M.A., 141: 1273 1949
72 ELLIS A Natural history of Bright's disease Clinical, histological and experimental observations I Nephritis Lancet, 1 1, 1942
73 ELLIS F A, AND BERESTON, E S Lupus erythematosus associated with pregnancy and menopause Arch Dermat & Syph, 65 170 1952
74 ENGMAN M F, JR Early acute lupus erythematosus Arch Dermat & Syph, 35: 685, 1937
75 ENTICKNAP, J B, AND JOINER, C L Bright's disease An attempt at a statistical assessment of the classification proposed by Ellis Brit Med J, 1: 1016, 1953
76 ERICHSEN, J Practical observations on some of the more important special diseases of the skin Lond Med Gaz, 36· 121, 1845
77 FAHEY, J L, LEONARD, E, CHURG, J, AND GODMAN, G Wegener's granulomatosis Am J Med, 17: 168, 1954
78 FISHBERG, A M Hypertension and Nephritis 5 ed Philadelphia Lea & Febiger 1954
79 FOX R A Disseminated lupus erythematosus—an allergic disease? Arch Path, 36: 311, 1943
80 FRERICH, C T The LE cell phenomenon in rheumatoid arthritis Master's Thesis, Graduate School, University of Minnesota
81 FRIEDLANDER D The aetiology of lupus erythematosus with especial reference to tuberculosis and a report of thirteen cases tested by the Moro reaction J Cutan Dis, 29: 417, 1911
82 FRIEDMAN, I A, SICKLEY, J F POSKE R M, BLACK, A, REEDER P S, KATZ, E, BRONSKY, D, HARTZ W, AND FELDHAKE, C The LE phenomenon in rheumatoid arthritis To be published

83 Fuchs C H Referred to by Veiel F Jadassohn s Handbuch der Haut und Geschlechtskrankheiten Bd X Teil 1 Berlin Springer 1931
84 Gairdner D The Schonlein Henoch syndrome (anaphylactoid purpura) Quart J Med 17 95 1948
85 Gale J C Electron microscope stud es of collagen from normal and diseased tissues Am J Path 27 455 1951
86 Galloway J and Macleod J M H Erythema multiforme and lupus erythematosus, their relationship to general toxemia Brit J Dermat 15 81 1903
87 Gennerich W Uber d e Atiologie des Lupus Erythematodes Arch f dermat u Syph, 135 184 1921
88 Gersh I Application in pathology of metl o l of fixation by freezing and drying of tissues Bull Internat A M Mus 28 179 1948
89 Gersh I Ground substance and the plasticity of connective tissues Harvey Lect 45 211 1949–1950
90 Ginzler J M and Fox T T Disseminated lupus erythematosus a cutaneous manifestation of a systemic disease (Libman-Sacks) Arch Int Med 65 26 1940
91 Godman G C and Churg J Wegener s granulomatosis Pathology and review of the literature A M A Arch Path 58 533 1954
92 Goeckerman W H Lupus erythematosus as a systemic disease J A M A 80 542 1923
93 Goeckerman W H and Montgomery H Lupus erythematosus an evaluation of histopathologic examinat ons Arch Dermat & Syph 25 304 1932
94 Goetz R H The pathology of progressive systemic sclerosis (generalized scleroderma) with special reference to the changes in the viscera Clinical Proceedings 4 337 1945
95 Gold S C Role of sulphonamides and penicillin in the pathogenesis of systemic lupus erythematosus Lancet 1 268 1951
96 Gold S C An hypothesis concerning the pathogenesis of systemic lupus erythematosus Brit J Dermat 65 43 1953
97 Gold S C and Gowing N I Systemic lupus erythematosus a clinical and pathological study Quart J Med 22 457 1953
98 Goldring W and Chasis H Hypertension and Hypertensive Disease New York The Commonwealth Fund 1944
99 Gore I Disseminated arteriolar and capillary platelet thrombosis A morphologic study of its histogenesis Am J Path 16 155 1940
100 Gould R G Sterol metabolism and its control Symposium on Atherosclerosis National Academy of Sciences 153 1955
101 Graffin J W Taylor C B and Hass C M A clinical and pathologic study of disseminated lupus erythematosus M Clin North America 33 79 1949
102 Griffith G C and Vural I L Acute and subacute disseminated lupus erythematosus correlation of clinical and postmortem findings in eighteen cases Circulation 3 492 1951
103 Gross L The cardiac lesions in Libman-Sacks disease with a consideration of its relationship to acute diffuse lupus erythematosus Am J Path 16 375 1940
104 Gueft B and Laufer A Further cytochemical studies in systemic lupus erythematosus A M A Arch Path 57 201 1954
105 Gunsett A Ist der Lupus erythematodes ein tuberkulid? Munch med Wchnschr., 50 378 1903
106 Hallopeau M Case report in Letter from Paris by Wickman L Brit J Dermat., 4; 123 1892
107 Hamburger J Goddé-Jolly D Pean V and Zambrowski S Les néphrites malignes avec lupus erythémateux aigu J d'Urologie 56: 261 1950
108 Hargraves M M Production in vitro of the L E cell phenomenon use of normal bone marrow elements and blood plasma from patients with acute disseminated lupus erythematosus Proc Staff Meet Mayo Clin 24 234 1949

109 HARGRAVES M M RICHMOND H AND MORTON R Presentation of two bone marrow elements the Tart cell and the L E cell Proc Staff Meet Mayo Clin, 23 25 1948

110 HARVEY A M SHULMAN L L TUMULTY P A CONLEY C L AND SCHOENRICH E H Systemic lupus erythematosus review of the literature and clinical analysis of 138 cases Medicine 33 291 1954

111 HASERICK J R Effect of cortisone and corticotropin on prognosis of systemic lupus erythematosus Arch Dermat & Syph 68: 714 1953

112 HASERICK J R Modern concepts of systemic lupus erythematosus a review of 126 cases J Chron Dis 1 317 1955

113 HASERICK J R CORCORAN A C AND DUSTAN H ACTH and cortisone in acute crises of systemic lupus erythematosus J A M A 146 643 1951

114 HASERICK J R AND LONG R Systemic lupus erythematosus preceded by false positive serologic tests for syphilis presentation of five cases Ann Int Med 37 559 1952

115 HEBRA J *Ztschr der k k Ges der Aerzte in Wien 1 40 1845*

116 HEBRA F AND ELFINGER A Atlas der Hautkrankheiten Braumuller Wein 1856

117 HEBRA F AND KAPOSI M K On diseases of the skin including the exanthemata Vol 6 Transl and ed by Warren Tay London The New Sydenham Society 1875

118 HELLER B I JACOBSON S E AND HAMMARSTEN J F The effect of cortisone in glomerulonephritis and the nephropathy of disseminated lupus erythematosus J Lab & Clin Med 37 133 1951

119 HENN M J PARKIN T W HARGRAVES M M AND ODEL H M Acute systemic lupus erythematosus syndrome from hydralazine hydrochloride A M A Arch Int Med 95 857 1955

120 HIJMANS W KLEVITS J H AND SCHUIT H R Ziekten met positief L E phenomeen Ned tschr geneesk 99 490 1955

121 HILLER A Practical Clinical Chemistry Springfield Ill Charles C Thomas 1953

122 JADASSOHN J Lupus erythematodes in Mracek F Handbuch der Hautkrankheiten Vol 3 Vienna Alfred Holder 1904

123 JADASSOHN J Dermatologie Wien Weidmann 1938

124 JAHIEL R AND JAHIEL R Local organ hypersensitivity to autogenous antigens experimental production of a pneumonitis J Allergy 21 10? 1950

125 JANEWAY C A *In discussion of paper by* Rich A R Tr A Am Phys 64 260 1951

126 JARCHO S a series of autopsied

127 JESSAR R rs of lupus erythematosus disseminatus Ann Int Med 38 717 1953

128 JONES D B AND LORING W F Glomerular thrombosis Am J Path 27 841 1951

129 JOSKE R A AND KING W E The L E Cell phenomenon in active chronic viral hepatitis Lancet 2 477 1955

130 KAISER I H Specificity of periarterial fibrosis of the spleen in disseminated lupus erythematosus Bull Johns Hopkins Hosp 71 31 1942

131 KAMPMEIER R H Vascular diseases due to hypersensitivity so-called diffuse collagen disease Am *Practit 1 113 1950*

132 KAPOSI M K Neue Beiträge zur Kenntniss des Lupus erythematosus Arch f Dermat u Syph 4 36 1872

133 KARK R M AND MUEHRCKE R C Biopsy of kidney in prone position Lancet 1: 1047

134 K

vestigation 34 ...

135 KARK R M MUEHRCKE R C PIRANI C L AND POLLAK V E *The clinical value of* renal biopsy Ann Int Med 43 807 1955

136 KEIL H Relationship between lupus erythematosus and tuberculosis a critical review based on *observations at necropsy* Arch Dermat & Syph 28 765 1933

162 LEE, S L, MICHAEL, S R, AND VURAL, I L The LE (lupus erythematosus) cell Am J Med, 10: 446 1951
163. LEFKOVITS, A M, AND FARROW, I J. The liver in rheumatoid arthritis Ann Rheum Dis, 14: 162, 1955
164 LEGGAT, P O, AND WALTON, E W Wegener's granulomatosis Thorax, 11: 94, 1956
165 LEINWAND, I, DURYEE, A W, AND RICHTER, M N Scleroderma (based on a study of over 150 cases) Ann Int Med, 41: 1003, 1954
166 LEITER, L Nephrosis Medicine, 10 135 1931
167 LIBMAN, E, AND SACKS, B A hitherto undescribed form of valvular and mural endocarditis Arch Int Med, 33: 701, 1924
168 LILLIE R D Histopathologic Technique Philadelphia The Blakiston Co, 1948
169 LINCOLN, M, AND RICKER, W A A case of periarteritis nodosa with L E cells, apparent complete remission with cortisone therapy Ann Int Med, 41: 639, 1954
170 LISTER L M, AND BAKER R D Needle biopsy of the kidney in the diagnosis of disseminated lupus erythematosus Am J Med, 17: 851, 1954
171 LITTLE G A case of lupus erythematosus Brit J Dermat, 17. 101 1905
172 LÖHLEIN M Ueber hämorrhagische Nierenaffektionen bei chronischer ulzeroser Endokarditis (Embolische nichteiterige Herdnephritis) Med Klin, 6 374, 1910
173 LOW, R C, AND RUTHERFORD, A Postmortem report of a case of lupus erythemaotosus Brit J Dermat, 32 362, 1920
174 LUDY, J B, AND CORSON, E F Lupus erythematosus Increased incidence, hematoporphyrinuria and spectroscopic findings Arch Dermat & Syph, 37: 403 1938
175 MACLEOD J M H Case of lupus erythematosus associated with nephritis Brit J Dermat 20: 162, 1908
176 MADDEN J F Acute disseminated lupus erythmatosus Arch Dermat & Syph, 25. 854, 1932
177 MALLORY F B Pathological Technique Philadelphia W B Saunders Co 1942
178 MARMONT A Value and limitations of the L E cell test in the syndrome known as [illegible]
179 [illegible] Vir-
180 [illegible] lpus erythematosus Arch f Dermat u Syph, 177: 223, 1938
181 MAXIMOW A A, AND BLOOM, W A Textbook of Histology 6th ed Philadelphia W B Saunders Co 1952
182 McCOY F W, PATTERSON M AND FREYBERG, R H A study of disseminated lupus [illegible]
[illegible] 1950
184 MERRELL M, AND SHULMAN, L E Determination of prognosis in chronic disease, illustrated by systemic lupus erythematosus J Chronic Dis, 1: 12 1955
185 MIALE J B Characteristic urinary findings in visceral angiitis (periarteritis nodosa and lupus erythematosus) Am J Clin Path, 17: 820, 1947
186 MICHEL H O Electrometric method for the determination of red blood cells and [illegible] esterase activity Federation Proceedings 8. 299, 1949
[illegible]
190 MONTGOMERY, H Disseminate lupus erythematosus [illegible] Medicine, Vol 4, 41 New York, Oxford University Press 1949

191 MONTGOMERY H, AND MCCREIGHT, W G Disseminate lupus erythematosus Arch Dermat & Syph 60 356 1949

192 MONTGOMERY, P O B AND MUIRHEAD E L Fibrinoid and hyalin a differentiation according to characteristics Am J Path 32: 613 1956

193 MOOK W H WEISS R S AND BROMBERG L K Lupus erythematosus disseminatus Arch Dermat & Syph 24 786 1931

194 MOOLTON S E AND CLARK E Viremia in acute hemolytic anemia and in autohemagglutination Arch Int Med 89: 270 1952

195 MOORE H C AND SHEEHAN H L The kidney of scleroderma Lancet I 68 1952

196 MOORE J E AND LUTZ W B The natural history of systemic lupus erythematosus an approach to its study through biologic false positive reactors J Chron Dis I 297 1955

197 MOSCHCOWITZ E An acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries An undescribed disease Arch Int Med 36 89 1925

198 MOVAT H Z AND MORE R H The nature and origin of fibrinoid Am J Path 32 611 1956

199 MUEHRCKE R C KARK R M AND PIRANI C L Technique of percutaneous kidney biopsy in the prone position J Urol 74 267 1955

200 MUEHRCKE R C KARK R M AND PIRANI C L Biopsy of the kidney in the diagnosis and management of renal disease New England J Med 253 537 1955

201 MUEHRCKE R C KARK R M PIRANI C L AND POLLAK V E The natural history of "lupus nephritis Clin Res Proc 3 139 1955

202 MUEHRCKE R C KARK R M PIRANI C L POLLAK V E AND STECK I E The histological and clinical evolution of lupus nephritis Ann Rheum Dis 14 371 1955

203 MUEHRCKE R C KARK R M PIRANI C L AND SCHOENBERGER J A Serial kidney biopsy studies in patients with the nephrotic syndrome J Lab & Clin Med 44 901 1954

204 MUIRHEAD E E CRASS G AND HILL J M Diffuse platelet thrombosis with thrombocytopenia and hemolytic anemia (thrombotic thrombocytopenic purpura) Am J Clin Path 18: 523 1948

205 NELIGAN J M Atlas of Cutaneous Diseases Dublin Fannin and Co 1855

206 NEUMANN F Beitrage zur Kenntniss des Lupus erythematosus Wien med Wchnschr 9: 613 1863

207 NEUMANN E Die Picrocarminfarbung und ihre Anwendung auf die Entzundungslehre Arch f Mikr Anat 25 130 1880

208 OBGYZLO M A Lupus erythematosus cell reaction its morphology and specificity Ann Rheum Dis 14: 414 1955

209 O'LEARY P Discussion on paper by Baehr and Pollack J A M A 134: 1173 1947

210 OLIVER J MACDOWELL M AND LEE Y C Cellular mechanism of protein metabolism in the nephron I The structural aspects of proteinuria tubular absorption droplet formation and the disposal of proteins J Exp Med 99: 589 1954

211 OLIVER J STRAUS W KRETCHMER N LEE Y C DICKERMAN H W AND CHEROT F Histochemical characteristics of absorption droplets in the nephron J Histochem & Cytochem 3: 277 1955

212 ORBISON J L Morphology of thrombotic thrombocytopenic purpura with demonstration of aneurysms Am J Path 28: 129 1952

213 OSLER W On a form of purpura associated with articular gastro intestinal and renal symptoms New York Medical Journal 48: 675 1888

214 OSLER W On the visceral complications of erythema exudativum multiforme Am J Med Sci 110: 629 1895

215 OSLER W The visceral lesions of the erythema group Brit J Dermat, 12 227 1900

216 OSLER W On the visceral manifestations of the erythema group of skin diseases Tr A Am Phys 18 599 1903

217 OSLER W On the visceral manifestations of the erythema group of skin diseases Am J Med Sci 127 1 1904

218 OSLER W The visceral lesions of purpura and allied conditions Brit Med J 1 517 1914

219 PAGEL W AND TREIP C S Viscero cutaneous collagenosis A study of the intermediate forms of dermatomyositis scleroderma and disseminated lupus erythematosus J Clin Path 8 1 1955

220 PATEK A J JR AND STETSON R P Hemophilia I The abnormal coagulation of the blood and its relation to the blood platelets J Clin Investigation 15 531 1936

221 PAUTRIER L M Lupus Erythemateux In Darier J Nouvelle Pratique Dermatologique Vol 3 Paris Masson et Cie 1936

222 PERNET G Le lupus erythemateux aigu d emblee Thesis Paris No 20 1908

223 PERRY H M JR AND SCHROEDER H A Syndrome simulating collagen disease caused by hydralazine (apresoline) J A M A 154 670 1954

224 PETERS J H The determination of creatinine and creatine in blood and urine with the photoelectric colorimeter J Biol Chem 146 179 1942

225 PIRANI C L AND BENNETT G A Rheumatoid arthritis A report of three cases progressing from childhood and emphasizing certain systemic manifestations Bull Hosp Joint Diseases 12 335 1951

[illegible] studies

2[illegible] I 1313 and 1372 1952

228 POLLACK A D [illegible] 29 859 1940

229 POLLAK V E [illegible] minated lupus erythematosus [illegible] stroenterology (in press)

230 POLLAK V E KARK R M PIRANI C L PELLOS P C AND STECK I E Unpublished observations 1956

231 POLLAK V E KARK R M PIRANI C L SHAFTER H AND MUEHRCKE R C Renal vein thrombosis and the nephrotic syndrome Am J Med, 21 496 1956

232 POLLAK V E PIRANI C L KARK R M MUEHRCKE R C FREDA V C AND NETTLES J B Reversible glomerular lesions in toxaemia of pregnancy Lancet 2 59 1956

233 POLLISTER A W AND LEUCHTENBERGER C The nature of the specificity of methyl [illegible] 1949

234 [illegible]

235 [illegible] iostasis Baltimore Charles C Thomas 1942

236 RAYER P Traite Theorique et Pratique des Maladies de la Peau Fonde sur de Nouvelles Recherches d Anatomie et de Physiologie Pathologiques Paris J B Bailliere 1826

237 REIFENSTEIN E C REIFENSTEIN E C JR AND REIFENSTEIN G H A variable symptom complex of undetermined etiology with fatal termination including conditions described as visceral erythema group (Osler) disseminated lupus erythematosus atypical verrucous endocarditis (Libman-Sacks) fever of unknown origin (Christian) and diffuse peripheral vascular disease (Baehr and others) Arch Int Med 63 553

238 [illegible]

239 [illegible] the

240 RICH A R BERTHRONG M AND B[illegible]

exper nt l and o ascular and renal l s ons produced l y anapl ylact c l ypersens ti ity B ll Jol ns Hopk ns Hosp 87 549 1950
211 Ric A R B rthson M Bennett I L Jr Cochran T H Griffith J C and McC D C The effect of ACTH an l cort sone upon exper mental glon erulo nephr t Tr A Am Ph s 64 ?5 1951
212 Rich A R and Gr gory J F l xper men al anapl ylact c les ons of coronary arter es of l rot typ commonly assoc ated w th rheumat c fever an l d sseminated l p s ryth m tos s Bull Jol ns Hopk ns Hosp 81 312 194
213 Ri hard D C Thr e cases of coll g n l sease treated w h cort co ds Br t M l J 2 ? ? 1951
214 R d an C I S rfiner C J and Black R J Renal invol ement in progress e s c sclero Cl n R s Proc 4 90 1956
21 R s l and Cold ne L C S eral le ons of a te d ssem nated l pus erythema to s M Cl n North Amer ca 19 333 1935
216 R I and Pill bury D M A te d sen n ted l l pus erythematosus s stem c l n Ann Int M d 12 9 1 1939
21 R e l a d Pillsbury D M L pus eryth natosus an l o ar an funct on observa n pos l le rel t on l j w h a rej ort of 6 cases Ann Int Med 21 10?? 1944
218 R S W and We ls B B S ste n c lup s er thematos s re ew of the l t rat e A J Cl n Path 23 139 1953
219 Ro nthe l C and Geraghty J T The phthalein te t an experimental an l cl n al st l of p len l ll onepl thalein n relat on to renal f n t on n health and l se A h Int M l 9 284 1912
?0 R s l M H Wi zell F W De ers R Sinclair R J G D thie J J R Atte d S M and Marrian G F Liver funct on n relation to possible abnormal t s f s lt tal ol n n rl eum to l arthr t s Ann Rh m D s 14 183 1955
2 1 Salvesen H A The eff t of blood tran fu ons n the k lney funct on f l one el l r s w l nen Acta Med Scan l na 131 337 1948
2 ? S tthe O l rsonal mm n cat on 19 6
? 3 S r e l W Th rol of the strep ococ s the et ology of pen ph g s l p s ryth at s an l erythema g oup of h c togen o s l rmatoses J M l g n M l al S t 36 2?? 193?
? 4 S tal s O and Schales S S S mple and a cura e e l od for l term na on of chlo r le n t of g nd fl l J B ol Chem 140 8 9 1941
255 S hr k C F Som ol s r a tons on telescop l r n ry sed nents Ann Int M l 12 8 1 s
256 S qu re J H and Bale s H L pus erythematos a cl n al st d of se nt s ne a s Br J D r t 14 36 190?
25 S I km n N H Swiler A I and Morr on M S n l on s m lat ng a e l se n t sd lup s eryth n to us appearan e after l y l alaz ne (apresol ne) th r p J A M A 155 149? 19 4
2 8 Shank R F and H wland C L Mod f ed meth od for q ant tat ve determ nat on of l l l v r t n of serum J B ol Ch m 162 131 1946
2 ? S e r M A and Libersky B D ssem nated l p s ryth ema s n al s of th rty fo r s Arch Int Med 90 ?0 19 2
?60 S fky M C nd Stafford D D Cl n al n e l od f r le es m t on of protein n r n an l l er l ool fl l Arch Int Med 32 2?? 1923
?61 S rt T S l l ase fa tal p servthem to B t J Dermat 19 ??1 190?
?6? S r I Thron bot c thron bocytope n c purp ra Ad ances n Internal Med ne C l l l d Do k W an l Snapper I The Year Book Publ l ers Inc Ch go
?63 S ocum C H D scus on on paper l y McCo et al (18?) Ann Rhe n D s 14 415 1955
?64 S ut l J I Th k ln v nt l p s erythematos s J I l B t ?0 41 1955

265 SNAPPER I Kidney trouble in acute lupus erythematosus in Berglund H and Medes G The Kidney in Health and Disease in Contributions by Eminent Authorities Philadelphia Lea and Febiger 1935

266 SOFFER L J AND BADER R Corticotropin and cortisone in acute disseminated lupus erythematosus results of long term use J A M A 149 1002 1952

267 SOFFER L J ELSTER S K AND HAMMERMAN D J Treatment of acute disseminated lupus erythematosus with corticotropin and cortisone A M A Arch Int Med 93 503 1954

268 SOFFER L J LEVITT M F AND BAEHR G Use of cortisone and adrenocorticotropic hormone in acute disseminated lupus erythematosus Arch Int Med 86 558 1950

269 SOFFER L J LUDEMANN H H AND BRILL G The effect of corticotropin and adrenal steroids on the management of acute disseminated lupus erythematosus Ann New York Acad Sci 61 418 1955

270 SPERRY W M AND WEBB M Revision of Schoenheimer Sperry method for cholesterol determination J Biol Chem 187 97, 1950

271 SQUIRE J R The nephrotic syndrome Brit Med J 2 1389 1953

272 STICKNEY J M The lesions of the kidneys in disseminated lupus erythematosus Master of Science Thesis Graduate School of the University of Minnesota 1939

273 STICKNEY J M Systemic involvement in disseminated lupus erythematosus Proc Staff Meet Mayo Clin 15: 680 1940

274 STICKNEY J M AND KEITH N M Renal involvement in disseminated lupus erythematosus Arch Int Med 66 643 1940

275 STOKES J H Transition sarcoid lupus erythematosus vs angiolupoid Arch Dermat & Syph 32 694 1935

276 STOKES J H BEERMAN H AND INGRAHAM N R JR The lupus erythematosus concept an attempt at integration Am J M Sc 207 540 1944

277 STUMPF G Zur Ätiologie des Lupus erythematodes Dermat Wchnschr 82 289 1926

278 SYMMERS W ST C Thrombotic microangiopathy Histological diagnosis during life Lancet 1 592 1956

279 SYMMERS W ST C AND BARROWCLIFF D F Platelet thrombosis syndrome J Path Bact 63 552 1951

280 SYMMERS W ST C AND GILLETT R Polyarteritis nodosa associated with malignant hypertension disseminated platelet thrombosis wire loop glomeruli pulmonary silicotuberculosis and sarcoidosis like lymphadenopathy A M A Arch Path 52 489 1951

281 TALBOTT J H CASTLEMAN B SMITHWICK R H MELVILLE R S AND PECORA L J Renal biopsy studies correlated with renal clearance observations in hypertensive patients treated by radical sympathectomy J Clin Investigation 22: 387 1943

282 TALBOTT J H GALL E A CONSOLAZIO W V AND COOMBS F S Dermatomyositis with scleroderma calcinosis and renal endarteritis associated with focal cortical necrosis report of case in which condition simulated Addison s disease with comment on metabolic and pathologic studies Arch Int Med 63 476 1939

283 TEILUM G Miliary epithelioid cell granulomas in lupus erythematosus disseminatus Acta Path Scandinav 22 73 1945

284 TEILUM G Pathogenetic studies on lupus erythematosus disseminatus and related diseases Acta Med Scandinav 123: 126 1946

285 TEILUM G Allergic hyperglobulinosis and hyalinosis (paramyloidosis) in reticulo-endothelial system in Boeck s sarcoid and other conditions morphologic immunity reaction Am J Path 24 389 1948

286 TEILUM G Hyperglobulinemia periarterial fibrosis of the spleen and wire loop lesion in disseminated lupus erythematosus in relation to allergic pathogenesis Am J Path

287

288 Thorn, G. W., Forsham, P. H., Frawley, T. F., Hill, S. R., Jr., Roche, M., Staehelin, D., and Wilson, D. L.: The clinical usefulness of ACTH and cortisone. New England J. Med. 242: 871, 1950.

289 Tremaine, M. J.: Similar to Libman-Sacks disease (polyserositis) with polyarteritis and glomerulonephritis: A report of 2 fatal cases. New England J. Med. 211: 754, 1934.

290 Tumulty, P. A.: The clinical course of systemic lupus erythematosus. J. A. M. A., 156: 947, 1954.

291 Tumulty, P. A., and Harvey, A. M.: The clinical course of disseminated lupus erythematosus; an evaluation of Osler's contributions. Bull. Johns Hopkins Hosp. 85: 47, 1949.

292 Van Slyke, D. D., and Neill, J. M.: The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. J. Biol. Chem. 61: 523, 1924.

293 Volk, R.: Periarteriitis nodosa bei einem Lupus erythematodes chronicus mit Exacerbationen. Dermat. Ztschr. 53: 682, 1928.

294 Volpé, R., and Hatch, J. T.: A case of scleroderma with L.E. cells and prolonged remission on cortisone therapy. Canad. M. A. J. 72: 597, 1955.

295 Vorhaus, L. J., and Kark, R. M.: Serum cholinesterase in health and disease. Am. J. Med. 14: 707, 1953.

296 Wagner, B. M.: Histochemical studies of fibrinoid substances and other abnormal tissue proteins. II. Effect of fibrinolytic enzymes. A. M. A. Arch. Path. 59: 63, 1955.

297 Wainwright, J., and Davson, J.: The renal appearances in the microscopic form of periarteritis nodosa. J. Path. & Bact. 62: 189, 1950.

298 Wakesin, B. H., and Mason, H. L.: The antigenicity of collagen. J. Immunol. 63: 427, 1949.

299 Wallace, D. C.: Diffuse disseminated platelet thrombosis (thrombotic thrombocytopenic purpura) with a report of two cases. M. J. Australia 2: 9, 1951.

300 Wilf, S. A., and Steege, P.: Thrombotic thrombocytopenic purpura. Review of the subject and report of three cases in children. Pediatrics 17: 882, 1956.

301 Wilens, S. L., and Stumpf, H. H.: Nodular and fatty glomerular lesions in rabbits on cortisone. Am. J. Path. 31: 275, 1955.

302 Willan, R.: Illustrations of Cutaneous Disease. London, H. Baillière, 1841.

303 Wilson, W. J. E.: A practical and theoretical treatise on the diagnosis, pathology and treatment of diseases of the skin arranged according to a natural system of classification and preceded by an outline of the anatomy and physiology of the skin. London, J. Churchill, 1842.

304 Wintrobe, M. M., and Landsberg, J. W.: A standardized technique for the blood sedimentation test. Am. J. M. Sc. 189: 102, 1935.

305 Wolfson, W. Q., Cohn, C., Calvary, E., and Ichiba, F.: Studies in serum proteins. V. A rapid procedure for the estimation of total protein, true albumin, total globulin, alpha globulin, beta globulin and gamma globulin in 1.0 ml. of serum. Am. J. Clin. Path. 18: 723, 1948.

306 Workes, B., and Ferson, R. D.: Hematoxylin bodies associated with allergic angiitis in absence of lupus erythematosus. Arch. Path. 56: 293, 1953.

307 Zeek, P. M.: Periarteritis nodosa and other forms of necrotizing angiitis. New England J. Med. 248: 764, 1953.